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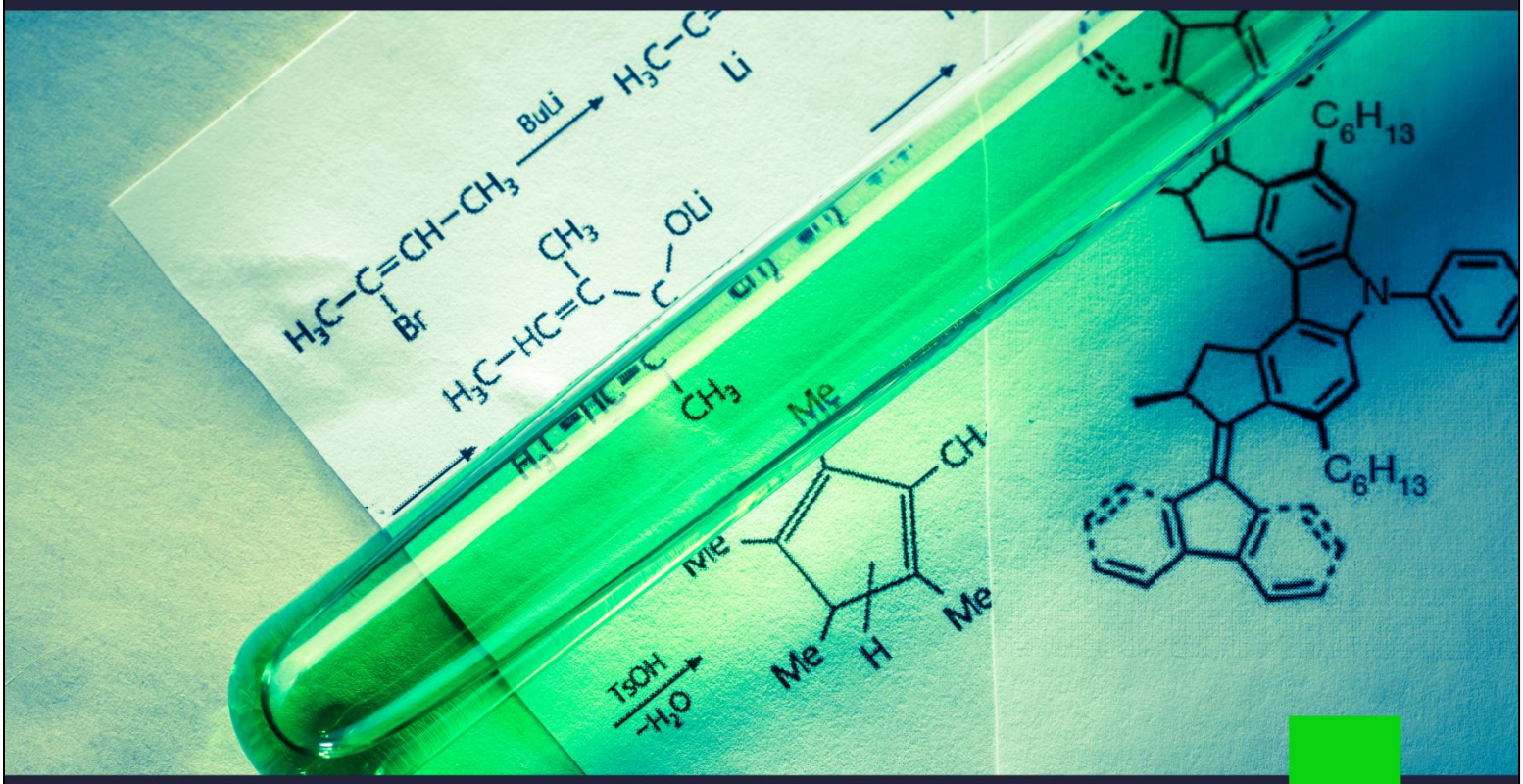

1,5-DISUBSTITUTED TETRAZOLES

SYNTHESIS AND CHARACTERIZATION

Dr. Suresh G. Vedpathak

Bhumi Publishing, India
First Edition: February 2025

1, 5-Disubstituted Tetrazoles:

Synthesis and Characterization

(ISBN: 978-93-48620-47-7)

Dr. Suresh G. Vedpathak

Professor and Head

Department of Chemistry,

S.M. Dnyandeo Mohekar Mahavidyalaya Kalamb,

Dist. Dharashiv. 413507 (MS) India

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PREFACE

Heterocyclic chemistry plays a vital role in modern organic synthesis, significantly contributing to the advancement of pharmaceuticals, agrochemicals, and materials science. Among the various heterocyclic compounds, tetrazoles have garnered immense attention due to their unique structural and electronic properties, which make them valuable in medicinal chemistry, catalysis, and coordination chemistry. This book, 1, 5-Disubstituted Tetrazoles: Synthesis and Characterization, provides a comprehensive exploration of the synthesis and structural characterization of 1, 5-disubstituted tetrazoles, highlighting novel synthetic methodologies and their potential applications.

The book begins with an Introduction to Heterocyclic Chemistry, offering a foundational understanding of heterocyclic compounds, their classification, and significance in organic synthesis. The focus then shifts to the Synthesis of 1, 5-Disubstituted Tetrazoles from Secondary Amides using Titanium Tetrachloride ($TiCl_4$), presenting an efficient and practical approach to tetrazole synthesis utilizing $TiCl_4$ as a key reagent.

Subsequent chapters delve into the targeted synthesis of substituted tetrazole derivatives. The Synthesis of Substituted (5-Methyl-1H-tetrazol-1-yl)benzenamines provides insights into the development of aromatic amines bearing the tetrazole moiety, which serve as versatile intermediates in pharmaceutical and material science applications. The Synthesis of Substituted 1, 2-Bis(4-(5-methyl-1H-tetrazol-1-yl)phenyl)-diazenes explores the preparation of diazene-linked tetrazole derivatives, which exhibit promising functional properties in molecular electronics and coordination chemistry. Finally, the Synthesis of Schiff Bases of Substituted (5-Methyl-1H-tetrazol-1-yl)benzenamines highlights the design and formation of Schiff base derivatives, expanding their potential for biological and catalytic applications.

This book aims to serve as a valuable resource for researchers, academicians, and students in the fields of organic chemistry, pharmaceutical sciences, and materials chemistry. By compiling state-of-the-art synthetic strategies and characterizations, it provides an essential reference for those interested in exploring the chemistry and applications of 1, 5-disubstituted tetrazoles.

I hope this book fosters further advancements in heterocyclic chemistry and inspires new research directions in the synthesis and functionalization of tetrazoles.

- Dr. Suresh G. Vedpathak

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It's golden opportunity for me to acknowledge genuine gratitude to Dr. Ashokrao Dnyadeo Mohekar, Secretary, Dnyan Prasarak Mandal Yermala, Former Management Council Member, Former Science Dean, Former Principal, S. M. Dnyandeo Mohekar Mahavidyalaya Kalamb for his continuous motivation, useful suggestions and guidance throughout my course of study.

I was blessed with an opportunity to express my unfathomable regards to my mentor Dr. R. A. Mane, Former Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, for his encouragement, guidance and co-operation throughout my educational career.

First of all, I would like to thank Dr. Babasaheb Ambedkar Marathwada University, Chhatrapati Sambhajinagar for giving me the opportunity to conduct this research work.

I am especially indebted to my father, Late Shri. Govardhan Vedpathak for his constant inspiration, encouragement and blessings.

I am especially indebted to my my mother, Smt. Chaturabai Vedpathak for her affection, inspiration, encouragement and blessings without which the present investigations could not have been completed. I also express my heartiest thanks to my wife Smt Shilpa & my daughters Sharayu and Tejasvi for emotional support & painstaking cooperation with their critical review was invaluable.

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I wish to thank my colleagues, and friends, for their academic support and valuable suggestions during the period of writing work. Once again I acknowledge our all family members and wish them to know that my thanks is not merely "proforma", they are sincerely offered and they well deserved.

- Dr. Suresh G. Vedpathak

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ABSTRACT

Heterocyclic compounds, especially, compounds with N, O-hetero atoms like triazole, pyrazole, oxazole, imidazole, benzimidazole, benzoxazole and tetrazole derivatives are found to be biologically active and consequently medicinally valuable compounds. It may attribute to the structural resemblance with several natural and synthetic molecules with biological activity.

The first chapter presents a concise account on chemistry of heterocyclic compounds with particular emphasis on 1, 5-disubstituted tetrazoles. Tetrazole derivatives have significant attention by the researcher because tetrazole scaffold act as bioisosteres of carboxylic acid, Tetrazoles have not been found in nature; with rare exceptions. These compounds do not exist in nature, but can be prepared artificially. They are resistant to biological degradation. This property makes it possible to use tetrazole as isosteric substituents of various functional groups in the development of biologically active substances. The tetrazolyl group has similar acidity to the carboxylic acid group and is almost allosteric with it, but is metabolically more stable at the physiologic pH.

The 1, 5-Disubstituted tetrazole moieties are found in numerous biologically active substances. Some of these scaffolds exhibit various types of biological properties, such as anti-inflammatory, antiviral, antibiotics, anti-ulcer, anti-tubercular, anti-hypertensive etc. 1, 5-Disubstituted tetrazole containing scaffolds are found to be used as drugs for various diseases. Some examples of such scaffolds are Vofopitant as an NK1 receptor antagonist; Cilostazol as a phosphodiesterase inhibitor, Cefazaflur as cephalosporin antibiotic etc.

In the second chapter, a facile general approach has made towards novel method for the synthesis of 1, 5-disubstituted tetrazoles have been designed to synthesize 1, 5-disubstituted tetrazoles form secondary amides using $TiCl_4$ as catalyst.

Aromatic amines and their derivatives are important functionalities, used as important starting materials for the manufacture of a variety of chemicals such as dyestuffs, pharmaceuticals, agrochemicals, surfactants, pesticides, polymers, etc. Chapter-III gives the novel route for the synthesis of 1, 5-disubstituted tetrazole containing anilines via multistep reactions.

Chapter IV describes the synthesis of some novel tetrazole containing symmetrical azobenzenes by controlled oxidation of 1, 5-disubstituted tetrazole containing anilines.

Chapter V describes the synthesis and characterization of three different series of novel tetrazole containing Schiff bases. Schiff bases were synthesized by condensation of 1, 5-disubstituted tetrazole containing anilines with aromatic aldehydes without catalyst at room temperature.

CHAPTER 1
INTRODUCTION TO HETEROCYCLIC COMPOUNDS

Introduction:

Heterocyclic chemistry represents the prevalent and diverse group of organic compounds which has started with the development of organic chemistry. Now a days, it has become one of the most composite and fascinating branches of organic chemistry and many versatile aspects are known that invade most of the aspects of modern organic, pharmaceutical, biochemical, agrochemical and other fields. Due to the wide range of structural diversity, the heterocyclic compounds have high degree of applications in biology[1], optics[2], electronics[3], material science[4], agriculture[5] and medicinal field. Thishas fascinated the workers from worldwide to discover and synthesize the large numberof organic compounds having heterocyclic ring adopting simple, safe, less energetic and eco-friendly methods.

Since from ancient time, heterocyclic compounds isolated from plants or animals are used as remedial agents. Heterocycles play a vital role in biochemical processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on aromatic heterocycles.[6] Heterocycles are present in many vitamins, natural products which show high degree of biological properties like antibacterial, antifungal, antipyretic, anti-inflammatory, antitubercular, anti-HIV, antiproliferative, antibiotic, antidiabetic, herbicidal, insecticidal etc.

Apart from natural resources, many of these compounds are synthesized by various methods. Certain modifications of these naturally occurring heterocycles by the addition of diverse substituents may lead to new products with better biological profile. Therefore the development of new chemical entities (NCEs) is the focus of intense activity in pharmaceutical industry. Natural and synthetic heterocycles are of immense importance to human life. Sugars and vitamin C are naturally occurring five or six membered heterocycles containing one oxygen atom. Quinine[7]**(1)** is the naturally occurring antimalarial while plasmoquine **(2)**, pentaquine **(3)** and chloroquine[8]**(4)** are synthetic antimalarials.

Most of the alkaloids contain nitrogenous heterocyclic ring systems. Tea and coffee contain the stimulating alkaloid caffeine. Naturally occurring camphothecin **(5)** is potent anticancer agent.[9] penicillins **(6)** and cephalosporins **(7)** are powerful antibiotics. Thiamin, riboflavin, nicotinic acid, folic acid, pyridoxine, biotin, vitamin-E, haemoglobin, chlorophyll, adenine, purine, pyrimidine, hormones etc. are heterocyclic in nature and play an important role in metabolic activities.

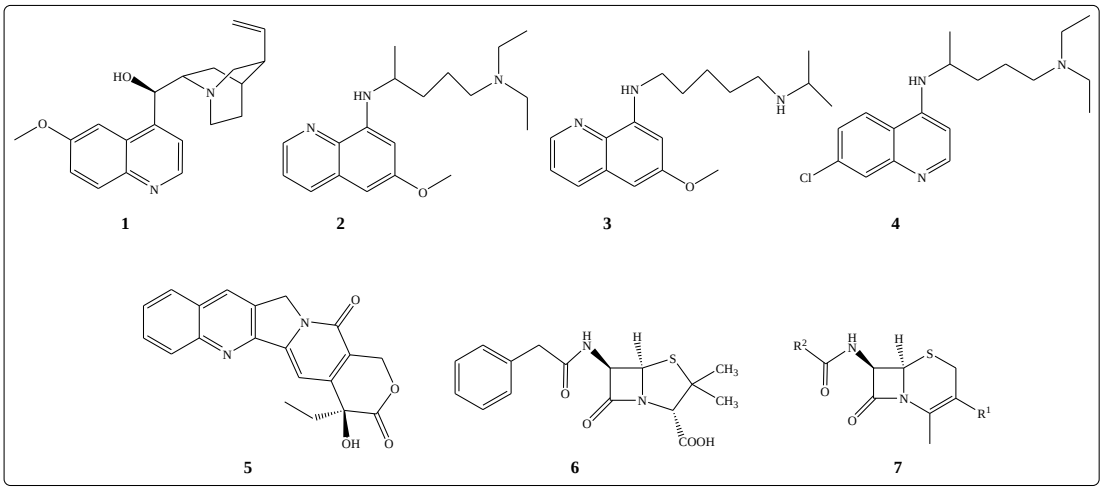
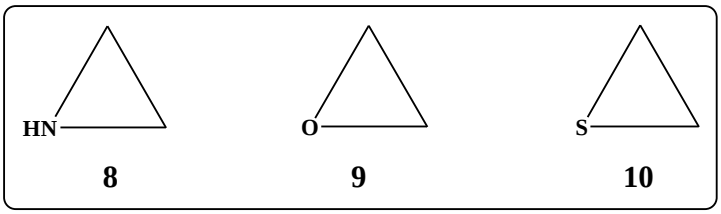


Fig. 1.1: Bioactive heterocycles

Many naturally occurring drugs are heterocyclic compounds including quinine, papaverine, atropine, procaine, codeine, morphine, etc. Synthetic drugs such ashypnotics, anticonvulsants, antihistamines, antithyroids, antiseptics, antipyretics, barbiturates, diazepam, metronidazole, azidothymidine etc are heterocyclic compounds. Pesticides like paraquat, diquat, simazine etc and insecticides like rotenome, diazinon, and minazon are heterocyclic compounds. Heterocyclic rings are constituent parts of synthetic dyes like mauveine. Some cyanins like melanin and cumarone are used to prepare polymeric plastics and resins. Piperideine is used as an antioxidant in rubber industry. Nitrone, dipyridiloxine, *o*-phenanthroline heterocycles are important and useful analytical reagents.

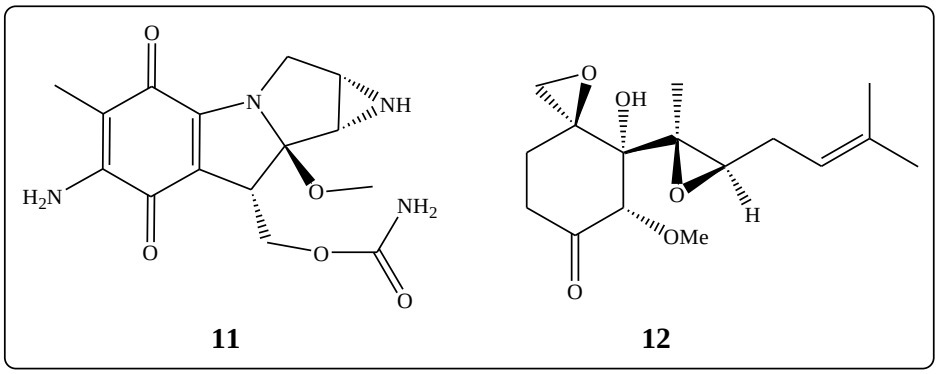
1.1 Classification of Heterocycles:

The major classes of heterocycles containing the common heteroatoms- nitrogen, oxygen, and sulfur- are reviewed in order of increasing ring size. The classification by ring size is convenient because heterocyclic rings of a given size have many common features.



The three membered ring heterocycles containing one heteroatom – nitrogen, oxygen or sulphur, are known as aziridine **(8)**, oxirane **(9)** and thiirane **(10)** respectively. These compounds are saturated heterocycles and due to the strain inherent in the three membered ring, they have comparable enhanced reactivity than the corresponding open chain amines, ethers, or sulphides. In medicine, aziridine and its derivatives are used for the treatment of cancer.[10] The most well-known class of natural products containing the aziridine ring is the mitomycin family **(11)** used as antitumor and antibiotics[11] as well. The naturally occurring compounds containing one or

more oxirane rings are biologically active and have promising therapeutic applications. e.g. the fungal product (-)-ovalicin **(12)**, which contains two oxirane rings, was found to be a nontoxic, non inflammatory and a more potent antiangiogenesis agent than the structural analogue of fumagillin. It inhibits selectively MetAP 2, which is related to many physiological activities such as angiogenesis.[12] An important synthetic oxirane having one ring is fosfomycin, used as an antibacterial drug; particularly used in the treatment of urinary tract infections. The compounds containing thiirane ring are more bactericidal and some of its derivatives have found to inhibit the growth of tuberculosis, whereas the oxides of thiirane have been reported as insecticides, molluscicides or herbicides.

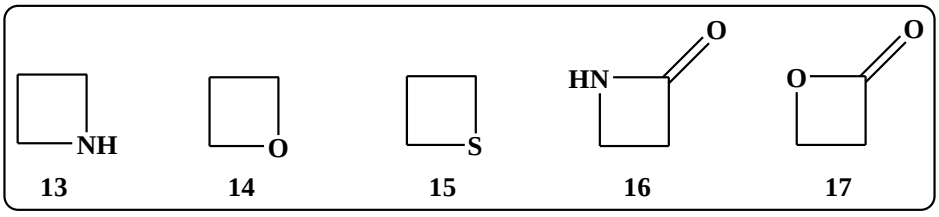


11 **12**

Since 1950, diaziridine (containing N-N), oxaziridine (O-N), thiaziridine (S-N), diozirane (O-O) and dithiirane (S-S) have been reported as three membered heterocycles having two heteroatoms. Despite from these, diaziridine and its derivatives are useful in the manufacture of plastic films and foamed plastic, and in the synthesis of anticancer drugs.

1.2 Four membered heterocycles

Azetidine, oxetane and thietane belong to four membered heterocycles containing one heteroatom as nitrogen, oxygen and sulphur respectively.

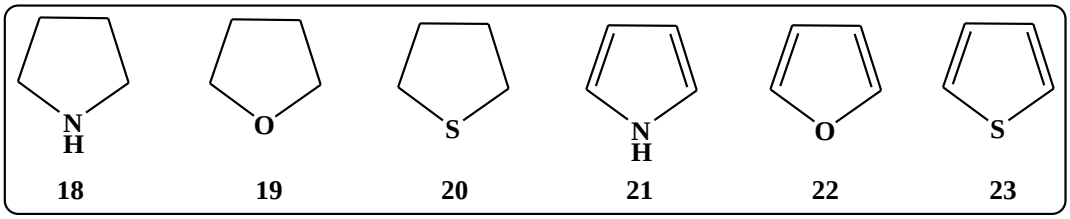


13 **14** **15** **16** **17**

The four membered heterocycles having nitrogen as heteroatom, i.e. azetidine show two related series of antibiotics, the penicillins and the cephalosporins. Both the series contain the azetidinone ring. The chemistry of azetidinones **(16)** was explored thoroughly during the intensive research into structure of penicillin. Oxetanones **(17)**, the structural analogues of azetidinones, are widely applied in manufacture of polymer and as herbicides, fungicides, and bactericides used in agriculture.

1.3 Five membered heterocycles

Pyrrolidine **(18)**, tetrahydrofuran **(19)** and thiophane **(20)** are five membered saturated heterocycles containing nitrogen, oxygen and sulphur as a heteroatom respectively, whereas pyrrole **(21)**, furan **(22)** and thiophene **(23)** are aromatic analogues respectively.



Pyrrole derivatives are widespread in the living world and are found among the alkaloids where nicotine is the well-known example which contains pyrrole ring. Haemoglobin **(24)** and related compounds such as myoglobin, the chlorophyll **(25)** are the light gathering pigments.

All carbohydrates are composed of one or more tetrahydrofuran ring system at equilibrium known as furanose. Ribose and deoxyribose sugars also constitute furanose form. Furfural, i.e. furan-2-carbaldehyde, is used extensively as solvent in the manufacture of plastic. The derivative of furan which occurs naturally is vitamin-C (**28)**.

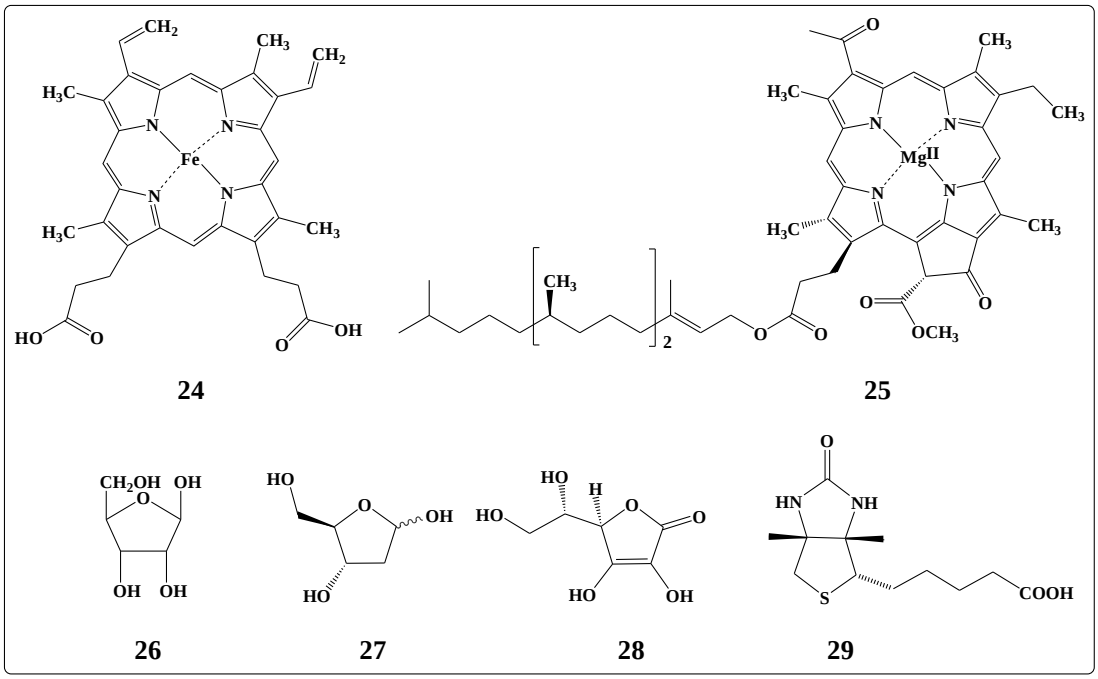


Fig. 1.2: The bioactive naturally occurring heterocycles

The sulphur containing five membered heterocycles, i.e. thiophene, and its derivatives are obtained from coal tar and crude petroleum. The most important biologically occurring thiophene derivative is the biotin **(29)**.

2. Azoles

A class of five membered nitrogen heterocycles containing at least one other non-carbon atom, i.e. nitrogen, sulphur or oxygen, is known as azoles. Azoles are aromatic in nature having two double bonds and one lone pair of electrons for aromatic bonding.

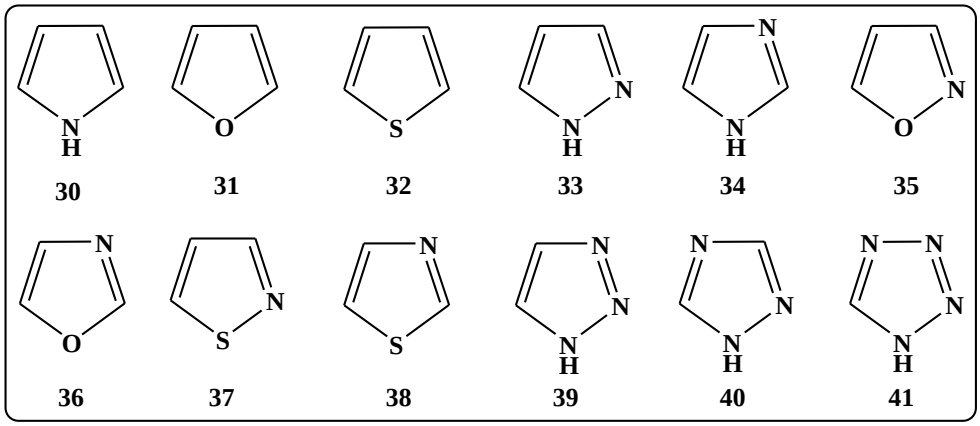
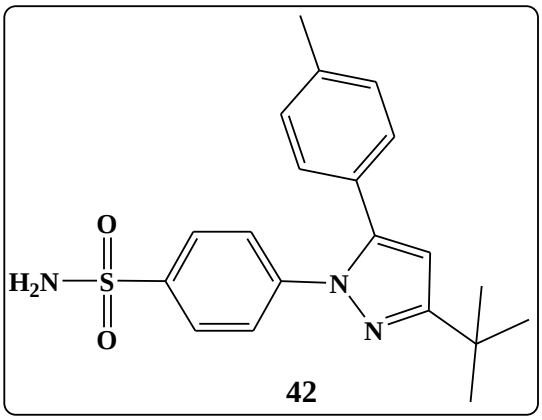


Fig. 1.3: Five membered heterocycles

The azoles containing one heteroatom as nitrogen, oxygen or sulphur are referred as pyrrole **(30)**, furan **(31)** or thiophene **(32)** respectively. The ring containing two nitrogen atoms at 1, 2-position is known as pyrazole **(33)** whereas the ring with two nitrogen atoms at 1, 3-position referred as imidazole **(34)**. The azoles containing two different heteroatoms are isoxazole **(35)**, oxazole **(36)**, isothiazole **(37)**, thiazole **(38)** etc. A five membered ring containing three nitrogen atoms is known as triazole as 1, 2, 3-triazole **(39)** and 1, 2, 4-triazole **(40)**. While azole containing four nitrogen atoms is known as tetrazole **(41)**. Apart from these, azoles when fused with benzene or other rings like pyrimidine, then these give different heterocyclic compounds e.g. imidazole when fused with benzene gives benzimidazole whereas with pyrimidine gives purine.

2.1. Pyrazole

Pyrazole is an organic compound that has the five membered aromatic heterocyclic rings with two nitrogen atoms at adjacent position. Many pyrazole derivatives have attracted considerable attention in the recent years for their diverse biological activities such as antifungal, [13-15] antimicrobial, [15] antipyretic, [16] anti-inflammatory, [17] antitumor, [18] antiproliferative, [19] Antiviral, [20] antidepressant and anticonvulsant, [21] antihyperglycemic, [22] CNS regulants, [23] and selective enzyme inhibitory activities. [24] A notable drug containing a pyrazole ring is Celecoxib **(42)**. Celecoxib is a COX-2 selective non-steroidal anti-inflammatory drug (NSAID). It is used to treat the pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation, and juvenile rheumatoid arthritis.[25]



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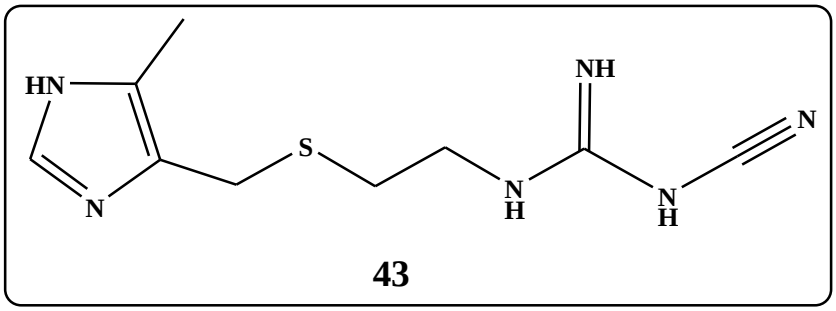
2.2. Imidazole

Imidazole is a planar five-member heterocyclic ring having three carbon and two nitrogen atoms with nitrogen atoms at 1st and 3rd positions. Imidazole was first synthesized by H. Debus in 1858, but various imidazole derivatives were discovered earlier in the 1840s. The imidazole ring is incorporated into many important biological molecules and is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Various literature surveys indicate that imidazole derivatives show various pharmacological activities like antifungal and antibacterial, [26] anti-inflammatory and analgesic, [27] antitubercular, [28] antidepressant, [29] anticancer, [30] antiviral, [31] antileishmanial.[32] Cimetidine **(43)** (Tagamet®, GSK) is an H2-receptor antagonist[33] which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn.[34]



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2.3. Triazole

In last few decades, triazole and its derivatives have come under considerable attention due to their increased synthetic and biological importance. The presence of three nitrogen hetero-atoms in five membered ring system defines an interesting class of compounds, the triazoles. It exists in two tautomeric forms, the 1, 2, 3-triazole **(39)** and the 1, 2, 4-triazole **(40)**. 1, 2, 4-triazole is considered to be pharmacologically important nucleus. Several compounds containing 1, 2, 4-triazole rings are well known as drugs. For example, vorozole **(44)**, letrozole **(45)**, and anastrozole **(46)** are non-steroidal drugs used for the treatment of cancer, [35] loreclezole **(47)** is used as anticonvulsant[36] while fluconazole **(48)** is used as an antimicrobial drug.[37]

Triazole derivatives are also used for the treatment of local and systemic fungal infections[38] and are also evaluated for antimicrobial, [39] antiviral, [40] antimalarial, [41] anti-histaminic, [42] and plant growth regulator anticoagulant activities.[43]

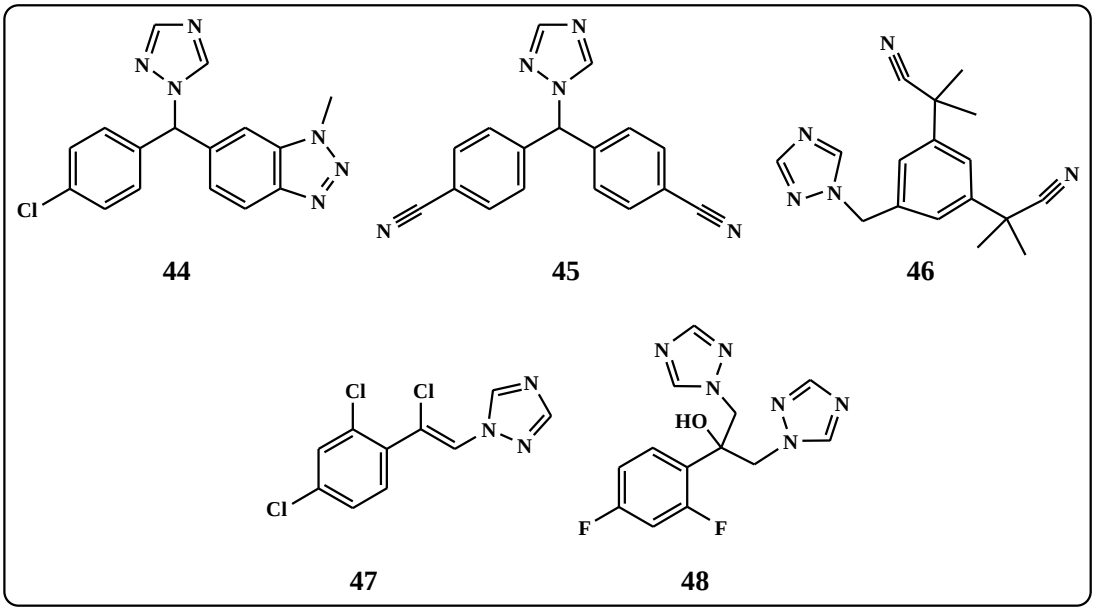
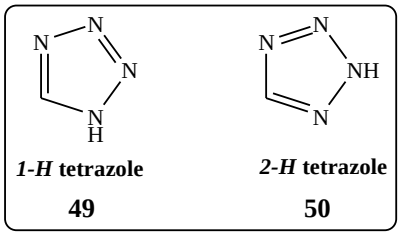


Fig. 1.4: The bioactive triazoles.

2.4. *1-H* Tetrazole

2.4.1 Introduction

The unsubstituted tetrazole having a molecular formula CH_2N_4 exists in two tautomeric forms, namely, 1-H tetrazole **(49)** and 2-H tetrazole **(50)** as shown below.



Tetrazoles are a class of synthetic organic heterocyclic compounds, considered unusual due to the presence of four nitrogen atoms in a five membered aromatic ring. Tetrazole was first prepared by the reaction of anhydrous hydrazoic acid and hydrogen cyanide under pressure. 5-substituted 1-H tetrazoles can be prepared from organic nitriles which react with sodium azide in presence of iodine or silica supported sodium bisulfate as a heterogeneous catalyst. Despite of high nitrogen content in a ring, the unsubstituted tetrazole and its derivatives show relatively good stability at room temperature or on heating or under microwave irradiation.

Tetrazoles have not been found in nature; with rare exceptions, these compounds do not exhibit appreciable biological activity, but they are at the same time resistant to biological degradation. This property makes it possible to use tetrazole as isosteric substituents of various functional groups in the development of biologically active substances. The tetrazolyl group has

similar acidity to the carboxylic acid group and is almost allosteric with it, but is metabolically more stable at the physiologic pH. Hence the tetrazole motif has been used in various pharmacophores as a suitable replacement of carboxylic acid moiety.

Tetrazoles have numerous applications in both material science and pharmaceuticals. Tetrazoles can tolerate a wide range of chemical environments, from strongly acidic to basic as well as oxidizing and reducing conditions. They also function as simple lipophilic spacers, displaying two substituents in the appropriate manner, where the connectivity patterns of the embedded tetrazole units bear a striking resemblance to those of their 1, 2, 3-triazole analogues.

2.4.2 Tetrazoles as Bioisosteres of carboxylic acid.

From the last two decades, tetrazole moiety has attracted a considerable attention as non-classical bioisostere of carboxylic acid group in biologically active molecules. The term non-classical isosterism refers to the concept in which functional groups that have similar physicochemical properties may be interchangeable, resulting in similar biological properties. Furthermore, a non-classical isostere may or may not have the same steric or electronic charactirstics, nor even the number of atoms, of the substituent for which it is used as a replacement. Tetrazoles are ionized at physiological pH and exhibit a planar structure like their carboxylic acid counterparts. However, Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylate while having similar acidity.[44] The increase in lipophilicity accounts for the higher membrane permeability that has seen with tetrazole bioisosteres. When substituted benzoic acids are compared with that of 5-substituted aryl tetrazole, it is found that tetrazoles are stronger acids than the corresponding benzoic acids. This is due to enhanced resonance stabilization of the aryl tetrazolate anion compared to the carboxylate anion. A retained pharmacological effect and a more favorable pharmacokinetic profile are often achieved by the replacement of carboxylate group with a metabolically stable tetrazolate group. The notable examples include PTB1B inhibitors, [45] mGlu 1 receptor agonists, [46] GHS, [47] etc.

Now a day, tetrazole and its derivatives are an increasingly popular functionality[48] with wide ranging applications. They have found use in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates, [49] in specialty explosives, [50] photography, and information recording systems, [51] not to mention as precursors to a variety of nitrogen containing heterocycles.[52] 5-substituted 1-H tetrazoles can be widely used for biological activities such as Alzheimer's disease, [53] analgesic, [54] antibacterial, [55] antiviral, [56] neurotransmittor, [57] COX-2 inhibitors, [58] antidiabetic[59] activities. They are also used a catalysts in various syntheses.

2.5. 1, 5-Disubstituted Tetrazoles.

Recently, the tetrazole ring has attracted significant attention, especially in medicinal chemistry, due to its isosteric nature with carboxyl group. The 1, 5-disubstituted tetrazoles were

incorporated into longer peptides as isosteres for the cis-amide bond.[60] These substituents have displayed similar types of biological activities because of their physicochemical properties, though they are structurally different. The replacement of the cis-amide group by 1, 5-disubstituted tetrazole enhances the metabolic stability of the molecule. The incorporation of tetrazole dipeptide analogues into biologically active peptides such as bradykinin, cholecystokinin, thyroliberin and somatostatin have been reported previously.

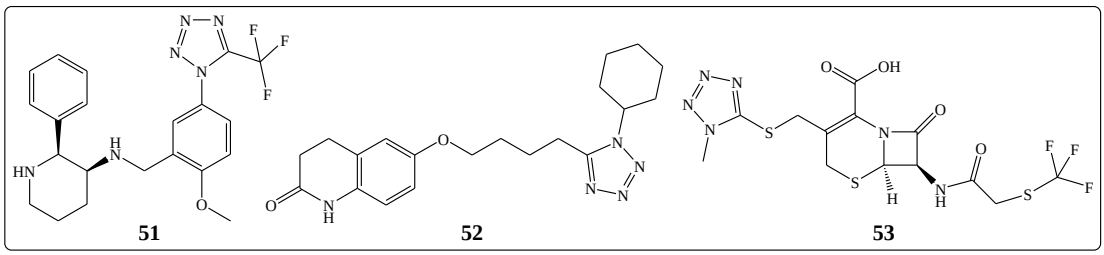


Fig. 1.5: 1, 5-Disubstuted tetrazole scaffolds as drugs

The 1, 5-Disubstituted tetrazole moieties are found in numerous biologically active substances. Some of these scaffolds exhibit various types of biological properties, such as anti-inflammatory, antiviral, antibiotics, anti-ulcer, anti-tubercular, anti-hypertensive etc. Now a days, 1, 5-disubstituted tetrazole containing scaffolds are found to be used as drugs for various diseases. Some examples of such scaffolds are Vofopitant **(51)** as an NK1 receptor antagonist; Cilostazol **(52)** as a phosphodiesterase inhibitor, Cefazaflur **(53)** as cephalosporin antibiotic, etc.

2.6. Biological Importance of 1, 5-disubstituted tetrazoles.

2.6.1. Antimicrobial Activity.

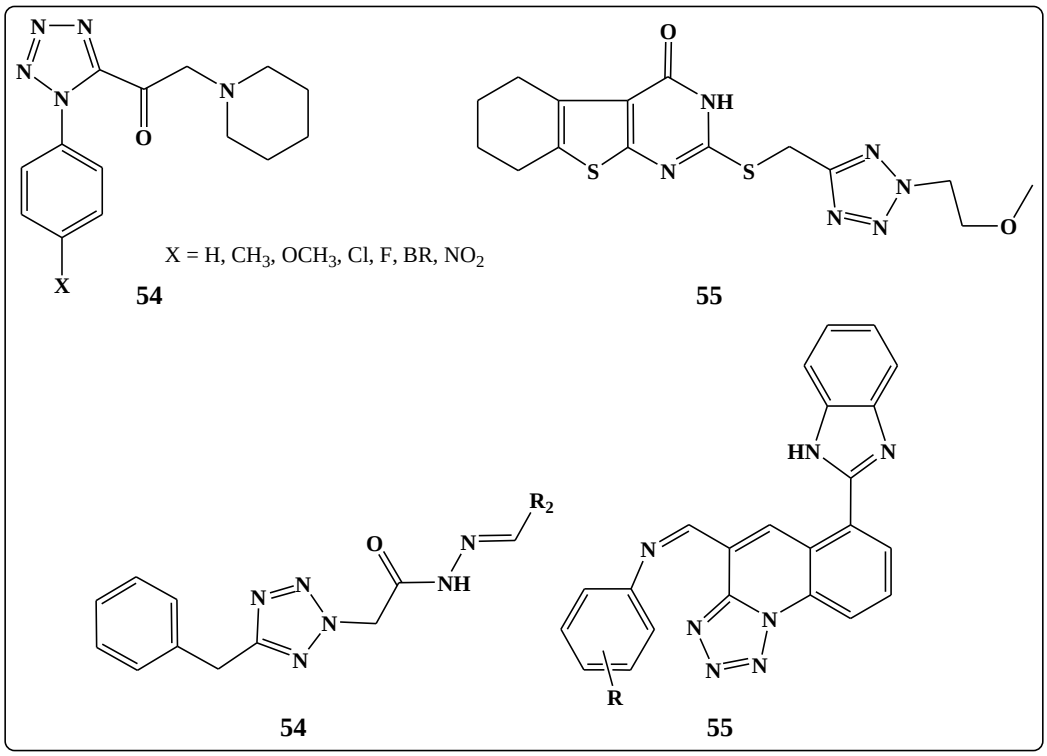


Fig. 1.6: 1, 5-Disubstituted tetrazole scaffolds as antimicrobials

Elavarasan T. et al[61] have reported the synthesis of a new series of novel heterocyclic compounds containing both tetrazoles and piperidine nuclei together, namely, 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperidin-1-yl)ethanone (**54**), and evaluated their antimicrobial activity using serial dilution method. The evaluation of antimicrobial activity shows that several compounds exhibit good activity when compared with the reference drug candidates and thus could be promising new lead molecules. *Ei-Sayed W.A. et al*[62] have synthesized a series of substituted 5, 6, 7, 8-tetrahydro-3*H*-benzo [4, 5]thieno[2, 3-d]pyrimidine-4-one derivatives **(55)** starting from 5, 6, 7, 8-tetrahydro-3*H*-benzo[4, 5]thieno[2, 3-d]pyrimidine-4-one derivatives. The antimicrobial activity of the prepared compounds against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus, Aspergillus niger* and *Candida albicans* were evaluated.

Kandeel S.H. et al[63] have synthesized a number of new substituted tetrazoles and their hydrazide derivatives as well as the corresponding sugar hydrazone derivatives **(56)** and tested for their antimicrobial activity against *Bacillus subtilis* (Gram-positive), *Pseudomonas aeruginosa* (Gram-negative), and *Streptomyces species* (Actinomycetes) and antifungal activity against four fungal strains namely, *Aspergillus flavus, Aspergillus fumigates, Penicillium marneffei and Trichophyton mentagrophytes*. The synthesized compounds displayed different degrees of antimicrobial activity. *Uttarwar R.B. et al*[64] have reported the synthesis of benzimidazolyl acetamide **(57)** and screened for their significant antimicrobial activity.

2.6.2. Analgesic Activity.

Kavitha H.P. et al[65] have reported the synthesis and analgesic activity of some novel tetrazole derivatives containing acridine ring **(58)**. Rajasekaran et al[66] have prepared a series of 5[b-(phenothiazinyl-10-yl)ethyl]-1-(acyl)-1, 2, 3, 4-tetrazoles **(59)** and demonstrated that these compounds possessed good analgesic activity tested both by acetic acid induced writhing method and hot plate method and anti-inflammatory activity tested by carrageenin induced paw edema method.

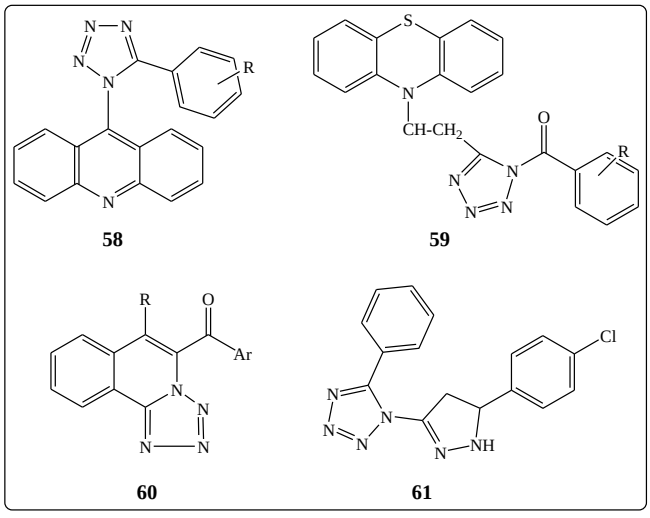


Fig. 1.7: 1, 5-Disubstituted tetrazole scaffolds as analgesics

Koppula et al[67] have synthesized a new series of triazole / tetrazole isoquinolines and coumarinoyl isocoumarin **(60)** derivatives and evaluated their antimicrobial activity against gram positive, gram negative bacteria and different fungi namely *F. pallidoroseum, C. capsici.* Synthesized compounds were also evaluated for their analgesic activity and tested compounds showed better results when compared with standard drug. *Bhaskar V.H. et al*[68] have synthesized eight different derivatives of substituted 5-phenyl-1-(5-substituted phenyl) -4, 5-dihydro-1*H*-pyrazol-3-yl)-1*H*-tetrazole **(61)** by reacting the chalcones with hydrazine hydrate in presence of glacial acetic acid. The compounds were screened for analgesic activity by acetic acid induced writhing method and hot plate method.

2.6.3. Antibacterial Activity.

Chauhan et al[69] have explored the synthesis of norfloxacin moiety by incorporating tetrazole scaffold at the N-4 position of the C-7 piperazin-1-yl group of newly developed norfloxacin entity, 1H-tetrazol-5-yl-(aryl) methyl piperazinyl-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid **(62)** and evaluated for their antibacterial activity against various strains of *Staphylococcus aureus*. All the synthesized compounds showed significant in vitro antibacterial activity against Gram-positive bacteria whereas some compounds displayed moderate activity against Gram-negative bacteria. *Sabbah M. et al*[70] have reported the synthesis of new analogues **(63)** of AHL, in which the amide was replaced by a triazole or tetrazole ring and tested for their activity as LuxR-dependent QS modulators. Several compounds showed a level of antagonistic or agonistic activity, notably some 1, 4-triazolic and 1, 5-tetrazolic derivatives.

Al-Juburi R.M.[71] has reported the synthesis of new tetrazole derivatives **(64)** from the reaction of the prepared Schiff bases with sodium azide in THF. Antibacterial activity of these compounds was determined by the ager diffusion method against *Echerchia Coli (G-)* and *Bacillus (G+). C.G. Dave et al*[72] have reported the antibacterial activity of all the newly synthesized tetrazolo[1, 5-*c*]pyrrolo[3, 2-e]pyrimidines **(65)** by the agar plate diffusion method.

Taha et al[73] have reported the synthesis of some heterocyclic compounds 1, 2, 4-Triazolo[4, 3-*d*]tetrazolo[5, 1-*f*]-1, 2, 4-triazines **(66)** utilizing Ethyl 1-Aminotetrazole-5-carboxylate and evaluated for their antimicrobial activity. Further, *Taha et al*[74] have reported the preparation of new compounds, substituted aryl tetrazolo[1, 5-b]1, 2, 5-oxadiazepin-9-ones **(67),** and evaluated for the antibacterial activities against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Escherichia coli* and *Klebsiella peneumoniae*) bacteria using Ciprofloxacin and Norfloxacin as antibacterial standards.

Sudhakar Babu K. et al[75] have reported the synthesis of a series of novel biphenyl tetrazoles **(68)** from the secondary amides and screened for their antibacterial activity. *Shanmugapandiyan et al*[76] have reported the synthesis of a new series of 2-(5-substituted phenyl-

1H-tetrazol-1-yl) pyridine **(69)** by the [3+2] cycloaddition of N-pyridyl-2-yl imidoformylchloride-benzene and sodium azide. All the synthesized compounds were screened for their antibacterial (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*) and antifungal activities (*Aspergillus fumigatus* and *Candida albicans*) by cup plate method. *Mohite P.B. et al*[77] have reported the synthesis of various tetrazole containing new pyrimidine 4-(substituted phenyl)-6-(5-phenyl-1*H*-tetrazol-1-yl) pyrimidin-2-ol **(70)** and evaluated for their in vitro antibacterial and antifungal properties.

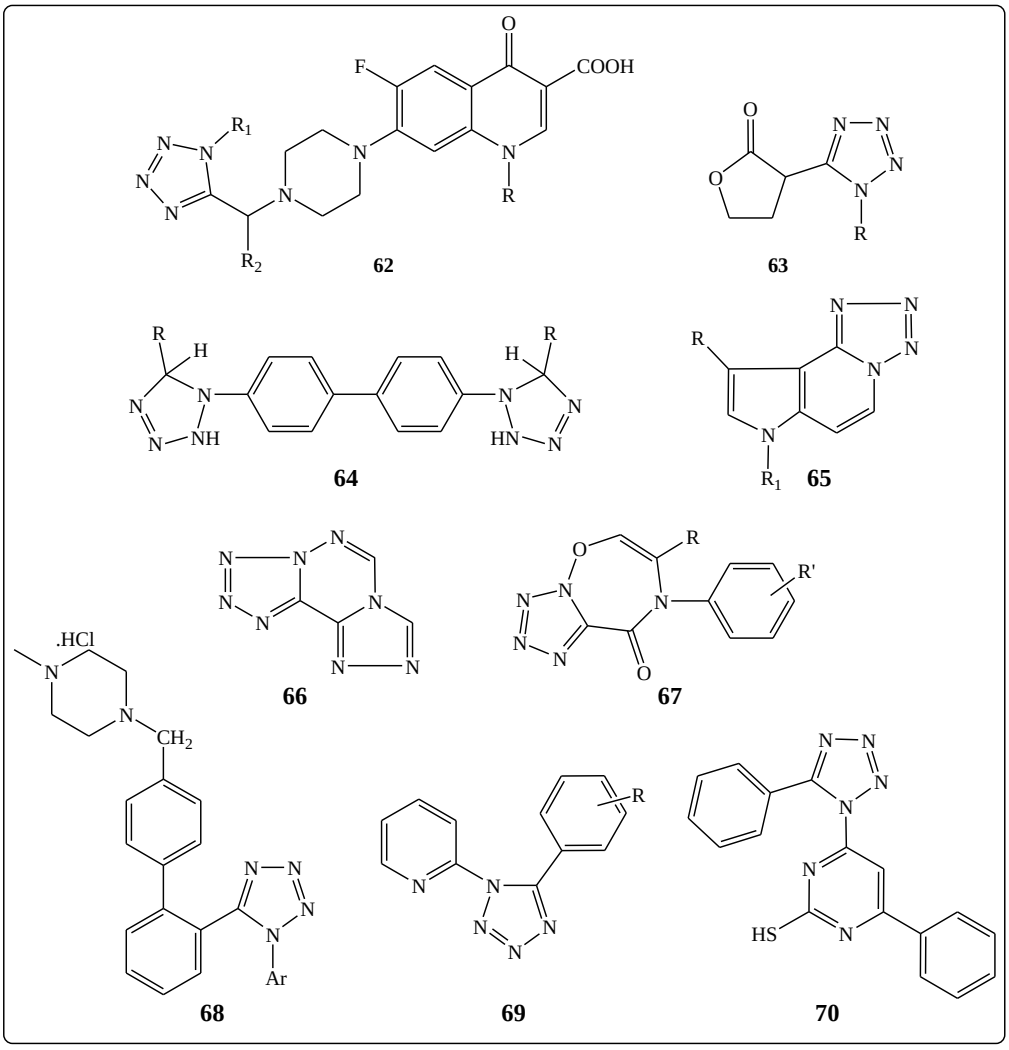


Fig. 1.8: 1, 5-Disubstituted tetrazole scaffolds as antibacterials

2.6.4. Antifungal Activity.

A series of (2R, 3S)-2-(2, 4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-2-yl)-1-[1, 2, 4]-triazol-1-yl-butan-2-ol (3a–n) and (2R, 3S)-2-(2, 4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazole-1-yl)-1-[1, 2, 4]-triazol-1-yl-butan-2-ol (4a–n) has been synthesized *by Upadhayaya et R.S. al*.[78] The antifungal activity of compounds was evaluated by *in vitro* agar diffusion and broth dilution assay. Compound **(71)** and its positional isomer **(72)** having 3-trifluoromethyl substitution on the phenyl ring of piperazine demonstrated

significant antifungal activity against variety of fungal cultures (Candida spp. *C. neoformans* and *Aspergillus spp.*). The compound **(72)** showed MIC value of 0.12 µg/mL for *C. albicans*, *C. albicans* V-01-191A-261 (resistant strain); 0.25 µg/mL for *C. tropicalis*, *C. parapsilosis* ATCC 22019 and *C. krusei* and MIC value of 0.5 lg/mL for *C. glabrata*, *C. krusei* ATCC 6258, which is comparable to itraconazole and better than fluconazole. Furthermore, *Upadhayaya R.S. et al*[79] have reported the synthesis of tetrazole-based triazole derivatives bearing an ethyl chain linked with an aryl-piperazine, which are structurally similar to compounds **(71)** and **(72)**, and evaluated for their antifungal activity against the different fungal cultures such as *Candida* species, *C. neoformans* and *Aspergillus* species.

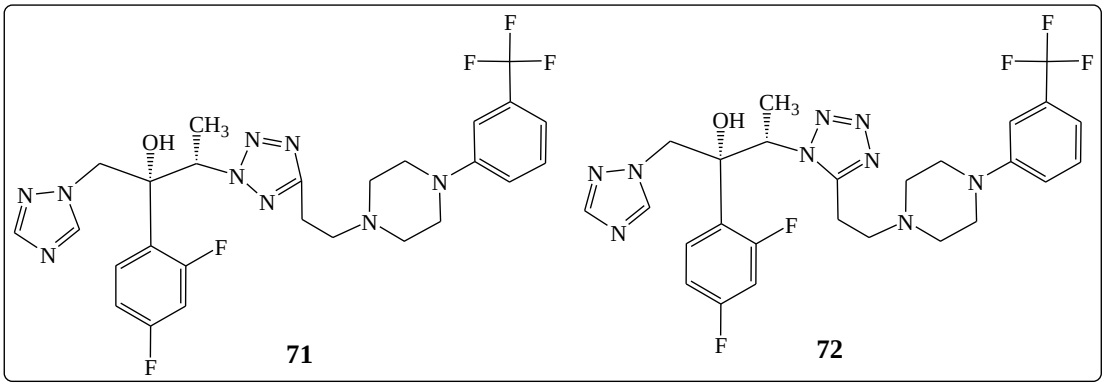


Fig. 1.9: 1, 5-Disubstituted tetrazole scaffolds as antifungals

2.6.5. Antibacterial and Antifungal Activity.

Pati et al[80] have prepared a variety of derivatives of 1-benzyl-5-(propylthio)-1*H*-tetrazole from 1-benzyl-5-[(3-bromopropyl)thio]tetrazole **(73a)**. All the synthesized compounds were screened for their antibacterial and antifungal activities. Among these some compounds showed growth inhibition towards *S. aureus* and *E. coli*, and pronounced growth inhibition for *P. aeruginosa* and *K. pneumoniae*. It was observed that most of the compounds exhibited good antifungal activity. Whereas some compounds showed good antifungal activity against *A. flavus*, *A. fumigatus*, *P. marneffei* and *T. menta-grophytes*.

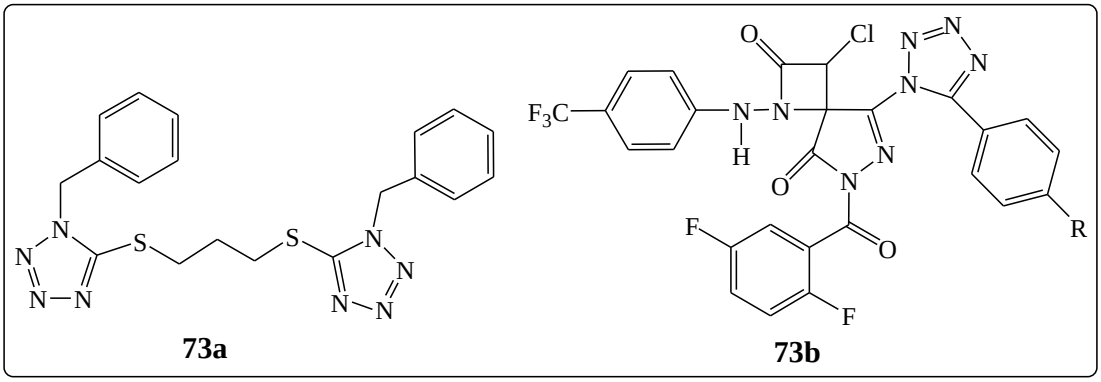


Fig. 1.10: Antibacterial and antifungal activity of 1, 5-disubstituted tetrazole scaffolds

Sudhakar Babu K. et al[81] have been synthesized a new novel derivatives of 3-chloro-6-(2, 5-difluorobenzoyl)-8-(5-(4-substitutedphenyl)-1H-tetrazol-1-yl)-1-((4-(trifluoromethyl) phenyl) amino)-1, 6, 7-triazaspiro[3.4]oct-7-ene-2, 5-dione **(73b)**. These compounds were screened for the antibacterial activity against the *S.* aureus (gram positive) and *E. coli* (gram negative) organisms and antifungal activity was screened against *A. Niger* and *C. albicans*. The presence of chloro, bromo or nitro group in the structure has shown increased effect on both the activities.

2.6.6. Antibacterial, Antifungal, Antimycobacterial & Anticancer Activity.

Adamec J. et al[82] have reported the synthesis of new hybrid molecules **(74)** of estrone containing tetrazole ring linked to estrone by n-heptyl bridges. The compounds with charge on molecule (the hybrid pyridinium or benzylsulfanylpyridinium salts) exhibited significant biological activity viz. antibacterial, antimycobacterial, antifungal, and antiproliferative. The antimycobacterial activities of three different series of tetrazole derivatives with the same substituents on phenyl ring were compared. Amongst them, the 5-benzylsulfanyl-1-phenyltetrazoles were the most potent. *Antypenko L.M. et al*[83] have reported a novel tetrazolo[1, 5-c]quinazoline-5-thione S-derivatives and screened for antibacterial and antifungal activities (100 μg) against *E. coli, S. aureus, E. aerogenes, E. faecalis, P. aeruginosa, K. pneumoniae,* and *Candida albicans*. 2-(tetrazolo[1, 5-*c*]quinazolin-5-ylthio)-1-(4-tolyl)ethanone **(75)**, 3-(tetrazolo[1, 5-*c*]quinazolin-5-ylthio)propanoic acid **(76)** and related 3-metyl-butanoic acids showed lethal antitumor activity (1.0 μM) against the acute lymphoblastic leukemia cell line (CCRF-CEM), and substances **(75)** and **(76)** exhibited moderate anticancer properties inhibiting growth of the leukemia MOLT-4 and HL06-(TB) cell lines.

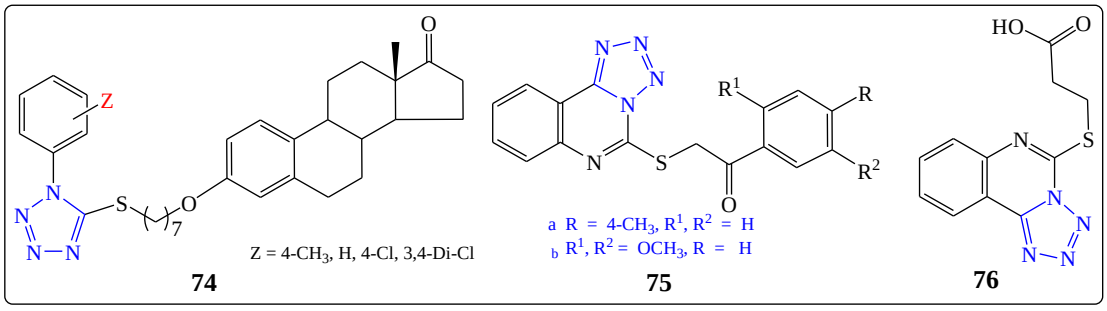


Fig. 1.11: Antibacterial, antifungal, antimycobacterial and anticanceractivity of 1, 5- disubstituted tetrazole scaffolds

2.6.7. Anti-convulsant Activity.

Rostom S. A.F. et al[84a] have reported the synthesis and antimicrobial evaluation of a new series of substituted tetrazoles **(77)** that are structurally related to the famous antimicrobial azole pharmacophore. Antimicrobial evaluation revealed that twenty compounds were able to display variable growth inhibitory effects on the tested Gram positive and Gram negative bacteria with special efficacy against the Gram positive strains. Meanwhile, six compounds exhibited moderate antifungal activity against *C. albicans* and *A. fumigatus*. On the other hand, out of

twelve compounds, two compounds were proved to be the most active anticonvulsant members with special high activity. *Wagle S. et al*[84b] have reported the synthesis of some new 4-styryltetrazolo[1, 5-*a*]quinoxaline **(78)** and screened for their in vitro potent anticonvulsant activity.

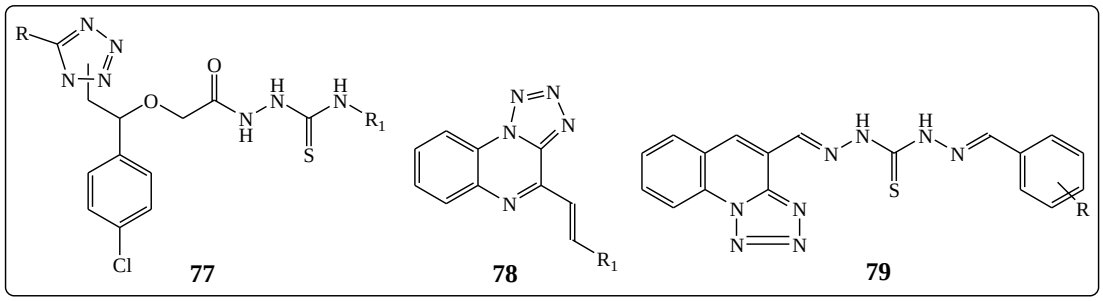


Fig. 1.12: 1, 5-Disubstituted tetrazole scaffolds as anticonvulsants

Sanjaykumar et al[84c] have synthesized a series of ten novel N″-[tetrazolo[1, 5-a]quinolin-4-ylmethylidene]thiocarbohydrazide derivatives **(79)** by the reaction of N″-[tetrazolo[1, 5-a]quinolin-4-ylmethylidene]thiocarbohydrazide with various substituted aromatic aldehydes. The newly synthesized compounds have been evaluated for their anti-oxidant (*In-vitro*) activity.

2.6.8. Antiviral Activity.

Wang S. X. et al[85] have reported the synthesis of a series of novel tetrazole containing 1, 2, 3-thiadiazole derivatives **(80)** via Ugi reaction. The preliminary bioassay indicated that most target compounds exhibited very good direct anti-TMV activity at 100 mg/mL, which was equal to or higher than that of ribavirin. Among them, compound 4l showed excellent anti-TMV activity with inhibition activity of 48.73%, which was higher than that of ninamycin.

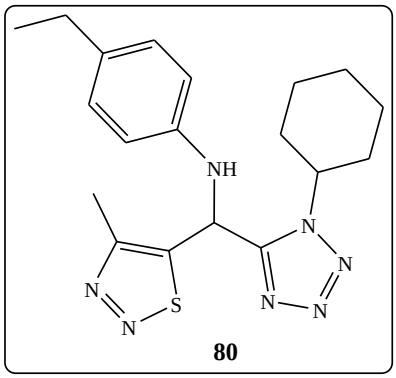


Fig. 1.13: 1, 5-Disubstituted tetrazole scaffolds as antiviral agents

2.6.9. Antiplasmodial Activity.

Tukulula M. et al[86] have designed and synthesized a small number of new arylamino quinoline tetrazole derivatives **(82a)** using the modified TMSN3-Ugi MCR and these were screened for antiplasmodial and antimycobacterial activities. The majority of these compounds exhibited modest activity against the 3D7 and K1 strains of *P. falciparum*, with IC50 values

ranging from 0.647 to 6.737 µM. In continuation of their work, *Tukulula M. et al*[87] have reported the synthesis of a series of new deoxyamodiaquine-based compounds **(82b)** via the modified $TMSN_3$-Ugi multi-component reaction and evaluated in vitro for antiplasmodial activity. The most potent compounds, 6a and 6b showed IC_{50} values in the range of 6–77 nM against chloroquine-resistant K1- and W2-strains of *Plasmodium falciparum*.

Tukulula M. et al[88] have designed and synthesized new nitroimidazole and nitroimidazooxazine derivatives and screened for antiplasmodial and antimycobacterial activity. The synthesized compounds, especially hybrids **(83a)** and **(83b)** exhibited potent activity against the K1 strain of *P. falciparum*, with IC_{50} values in the low micromolar range. Furthermore, compounds from the MCR series possessed superior antimycobacterial activity, with MIC99 values in the region of 0.25−125 µM. Furthermore, the majority of the active compounds were more efficacious than kanamycin, a standard TB drug, in these assays.

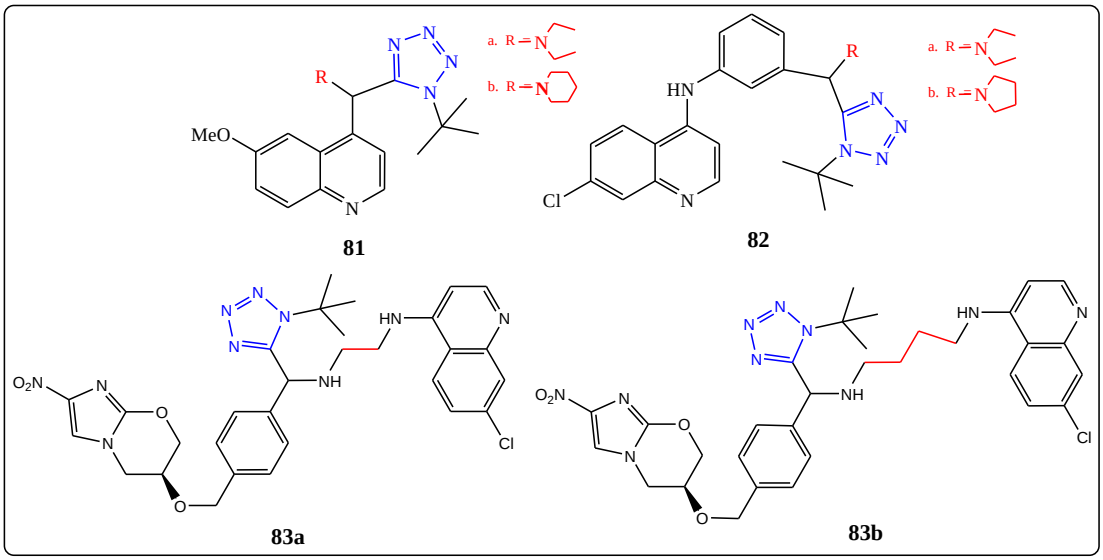


Fig. 1.14: 1, 5-disubstituted tetrazole scaffolds as antiplasmodials.

2.6.10. Anti-inflammatory Activity.

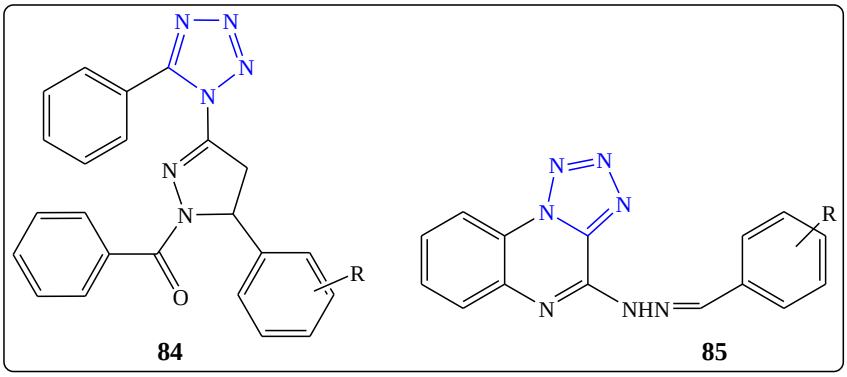


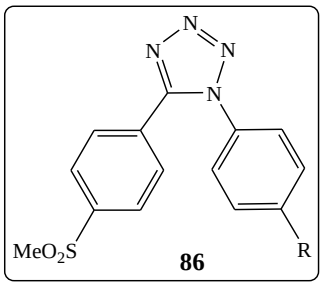
Fig. 1.15: 1, 5-disubstituted tetrazole scaffolds as anti-inflammatory agents

Mohite P.B. et al[89a] have synthesized [5-substitutedphenyl-3-(5-phenyl-1H-tetrazol-1-yl)-4, 5-dihydro-1H-pyrazol-1-yl] (pyridin-4-yl) methanone **(84)** from benzonitrile and screened for

in-vitro anti-inflammatory activity. *Natarajan U. et al*[89b] have described a novel synthetic route for the synthesis of Schiff's bases incorporating tetrazolo quinoxalines **(85)** and screened for their in vitro antimicrobial and anti-inflammatory activity.

2.6.11. COX-1 & 2 Inhibitor Activities.

Selective COX-2 inhibitors are a type of NSAID that directly target COX-2, an enzyme responsible for inflammation and pain. *B.J. Al-Hourani et al*[90] have synthesized a series of 1, 5-diaryl-substituted tetrazole derivatives **(86)** via conversion of readily available diaryl amides into corresponding imidoylchlorides followed by reaction with sodium azide and all compounds were evaluated for COX assays *in vitro* to determine COX-1 and COX-2 inhibitory potency and selectivity. In continuation of their work, *B.J. Al-Hourani et al*[91] have prepared a series of novel 5-substituted 1H-tetrazoles as COX-2 inhibitors via treatment of various diaryl amides with tetrachlorosilane/sodium azide.

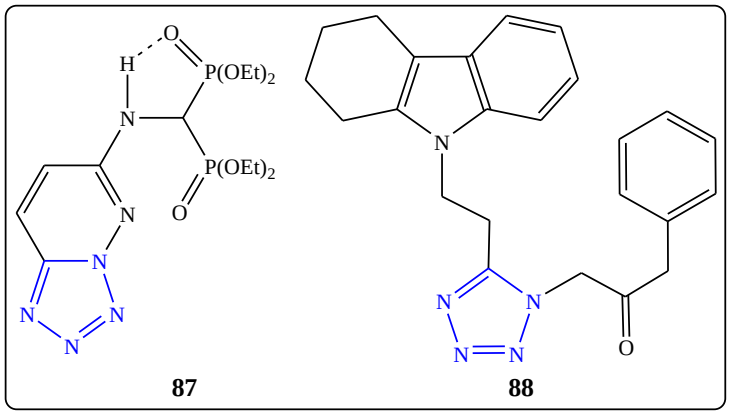


86

Fig. 1.16: 1, 5-disubstituted tetrazole scaffold as COX-1 & 2 Inhibitor.

2.6.12. Antinociceptive and anti-inflammatory Activity.

W. M. Abdou et al[92] have offered a practical and efficient procedure for the synthesis of imidazophosphor esters based tetrazolo[1, 5-*b*]pyridazine **(87)** in high yields by application of different types of HE reagents on 3, 6-diazidopyridazine. Among the products, the β-enaminobisphosphonate compound demonstrated the highest antinociceptive and the anti-inflammatory activities.



87 **88**

Fig. 1.17: 1, 5-Disubstituted tetrazole scaffolds as antinociceptive and anti- inflammatory agents

Rajasekaran et al[93] have synthesized twelve different derivatives of substituted-{5-[2-(1, 2, 3, 4-tetrahydrocarbazol-9-yl)ethyl]tetrazol-1-yl}alkanones by reacting 9-[2-(1*H*-tetrazol-5-yl)-ethyl]-2, 3, 4, 9-tetrahydro-1*H*-carbazole and the appropriate acid chlorides. The compounds were screened for antinociceptive activity by acetic acid induced writhing method and hot plate method. 1-Phenyl-2-{5-[2-(1, 2, 3, 4-tetrahydrocarbazol-9-yl)ethyl]tetrazol-1-yl}ethanone (**88**) was found to be the most active compound of the series.

2.6.13. CB1 Inhibitors.

S. Y. Kang et al[94] investigated a series of tetrazole-biarylpyrazole derivatives **(89)** for their inhibition of binding for CB1 and CB2 receptors. Several compounds in this series exhibited potent CB1 receptor binding affinities, validating the hypothesis that tetrazole could replace amide functionality to act as a bioisostere of amide moiety of rimonabant. G. Ortar et al[95] have synthesized a series of eighteen 1, 5- and 2, 5-disubstituted carbamoyl tetrazoles **(90)** and evaluated as inhibitors of endocannabinoid inactivation.

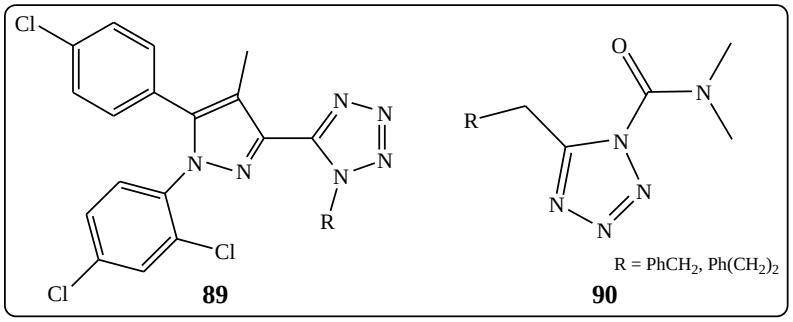


Fig. 1.18: 1, 5-disubstituted tetrazole scaffold as CB1 inhibitors.

2.6.14. Anti-HIV Activity.

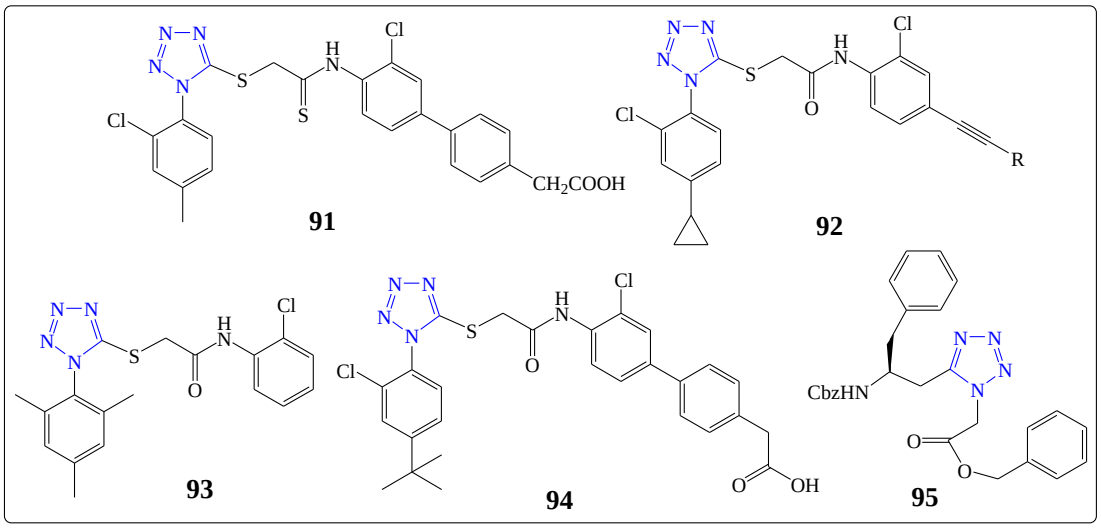


Fig. 1.19: 1, 5-Disubstituted tetrazole scaffolds as anti-HIV agents

The role of tetrazolyl group in the binding of the thiotetrazole acetanilide inhibitors with the HIV-1 reverse transcriptase has been studied through the design of different cyclic and acyclic tetrazole **(91)** replacements by *A. Gagnon et al*.[96] It was found that a simple Z alkene is

capable of retaining most of the potency against the WT-RT, supporting the hypothesis that the tetrazole partially acts as an orienting scaffold. Modeling studies of the tetrazolyl and NH-pyrazolyl inhibitors suggested important interactions between the heterocyclic linkers and residue 103, providing a rationale for the potency observed against both RTs. *A. Gagnon et al*[97] have, further reported the synthesis of a series of aryl thiotetrazolylacetanilides and evaluated as a potent inhibitors of the HIV-1 wild type and K103N/Y181C double mutant reverse transcriptases. *W. Li et al*[98] have reported the discovery of potent HIV-1 non-nucleoside reverse transcriptase inhibitors from arylthioacetanilide **(92)** structural motif.

Muraglia E. et al[99] have reported a series of aryltetrazolylacetanilides **(93)** and evaluated as HIV-1 non-nucleoside reverse transcriptase inhibitors on wild-type virus and on the clinically relevant K103N mutant strain. *O'Meara J.A. et al*[100] have identified a compound **(94)** as a potent, broad-spectrum, NNRTI inhibitor of HIV-1 replication. Analysis of the bond conformation of analogs of this inhibitor via molecular modeling and NMR contributed to the design of novel tertiary amide, carbamate, and thiocarbamate based NNRTIs. *May B.C.H. et al*[101] have synthesized a core dipeptidomimetic **(95)**, by replacing cis-amide bond of peptides with 1, 5-disubstituted tetrazoles as isostere, and evaluated for the potent HIV-protease inhibitors.

2.6.15. Anti-tubercular Activity.

Shanmugapandiyan P. et al[102] have synthesized several new 5-chloro-2-(5-(substituted phenyl)-1H-tetrazol-1-yl) pyridines **(96)** by reaction of 2- amino pyridine derivative with various aromatic acid chlorides and sodium azide. All the synthesized compounds were screened for their antitubercular activity by MABA method and have exhibited significant activity against *Mycobacterium tuberculosis* H37Rv. The activities expressed as the minimum inhibitory concentration (MIC) fall into the range of 3.125-25 µg/ml. *Mohite P.B. et al* [103] have reported the antimycobacterial activity of different tetrazoles **(97)** having different aryl substituent on azetidinone core against *Mycobacterium tuberculosis* strain H37Rv. Compounds having a 4-methoxyphenyl and 4-dimethylamino phenyl unit on azetidinone ring, are highly active when compared with isoniazid and rifampin. *Chauhan K. et al*[104] have described the synthesis and in vitro antitubercular activity of a novel series of thiazolone piperazine tetrazole derivatives **(98)**.

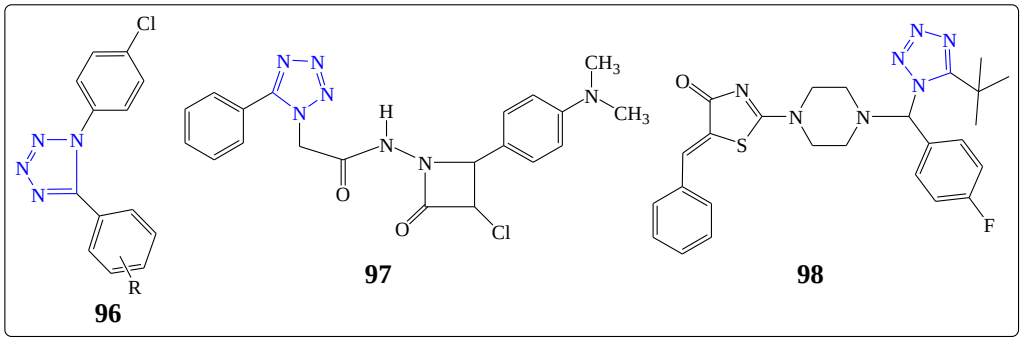


Fig. 1.20: 1, 5-disubstituted tetrazole scaffolds as anti-tubercular agents

2.6.16. Antitumor Activity

Hussein A.M. et al[105] have reported an easy and efficient route for the synthesis of some tetrazolo[1, 5-a]-pyrimidine derivatives. The derivative 6, 7, 8, 9-tetrahydrotetrazolo[1, 5-a]quinazoline **(99)** has profound anti-tumor cytotoxic effects against EAC both in vivo and in vitro and against HepG2 cell line in vitro. *Muralikrishna S. et al*[106a] have reported the synthesis of 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one **(100)** and tested *in vitro* for antitumor activity using the Alamar Blue assay.

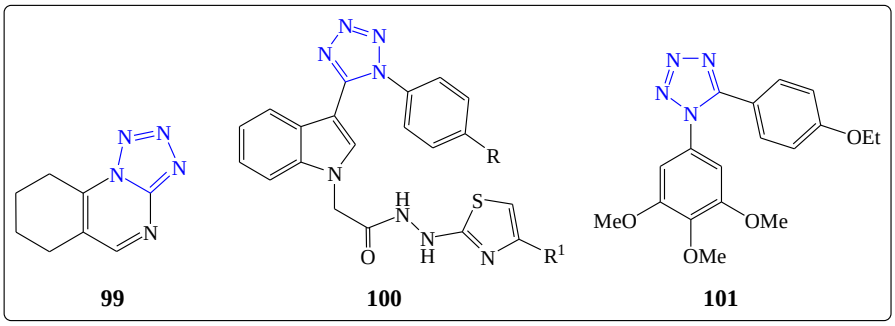


Fig. 1.21: 1, 5-disubstituted tetrazole scaffolds as anti-tumor agents

Romagnoli R. et al[106b] have concisely synthesized two series of 1, 5-diaryl substituted tetrazoles **(101)** as rigid analogues of Combretastatin and identified as potent antiproliferative and antitumor agents. Several of these compounds were found having potent activity in inhibiting the growth of multidrug resistant cells over expressing P-glycoprotein. Active compounds induced apoptosis through the mitochondrial pathway with activation of caspase-9 and caspase-3.

2.6.17. Anticancer Activity

An efficient synthetic route to the hydronaphthoquinone sulfonamide scaffold containing tetrazole **(102)** was developed by *Ge Y. et al.*[107] The synthesized scaffold was evaluated as proteasome inhibitor. The compound **(102)** was found effective in the accumulation of ubiquitinated cellular proteins and inhibition of tumor cell proliferation of breast cancer cells. *Li X.et al*[108] reported the design, synthesis, and biological evaluation of a new series of largazole analogues in which a 4-methylthiazoline moiety was replaced with a triazole and tetrazole ring, respectively. Compound **(103)** bearing a tetrazole ring was identified to show much better selectivity for HDAC1 over HDAC9 than largazole (10-fold).

Jedhe G.S. et al[109] have developed a series of 1, 5-disubstituted tetrazole analogues of combretastatin analogues with extended hydrogen-bond donors at the ortho-positions of the aryl A and B rings and evaluated for their inhibition of the growth of four different human cancer cell lines, that is, HeLa, human non-small-cell lung carcinoma (A549 and H1299), and MCF-7. Compound **(104)** bearing ortho-hydroxyl group in the B-ring was shown to enhance

antiproliferative activity. *Arshad M. et al*[110].have reported the synthesis of a series of tetrazolohydrazones compounds (1-14) starting from the simple chemical molecules. All the compounds were screened against the ER+/- breast cancer cell lines. Out of these, five compounds were found to retard the growth of breast cancer cells. Based on the gene study the compound **(105)** and two other were found more effective in retarding the growth of MCF-7 cells. While compound **(106)** showed more growth retarding effects in ER negative MDA-MB-231 and ZR-75 cell lines.

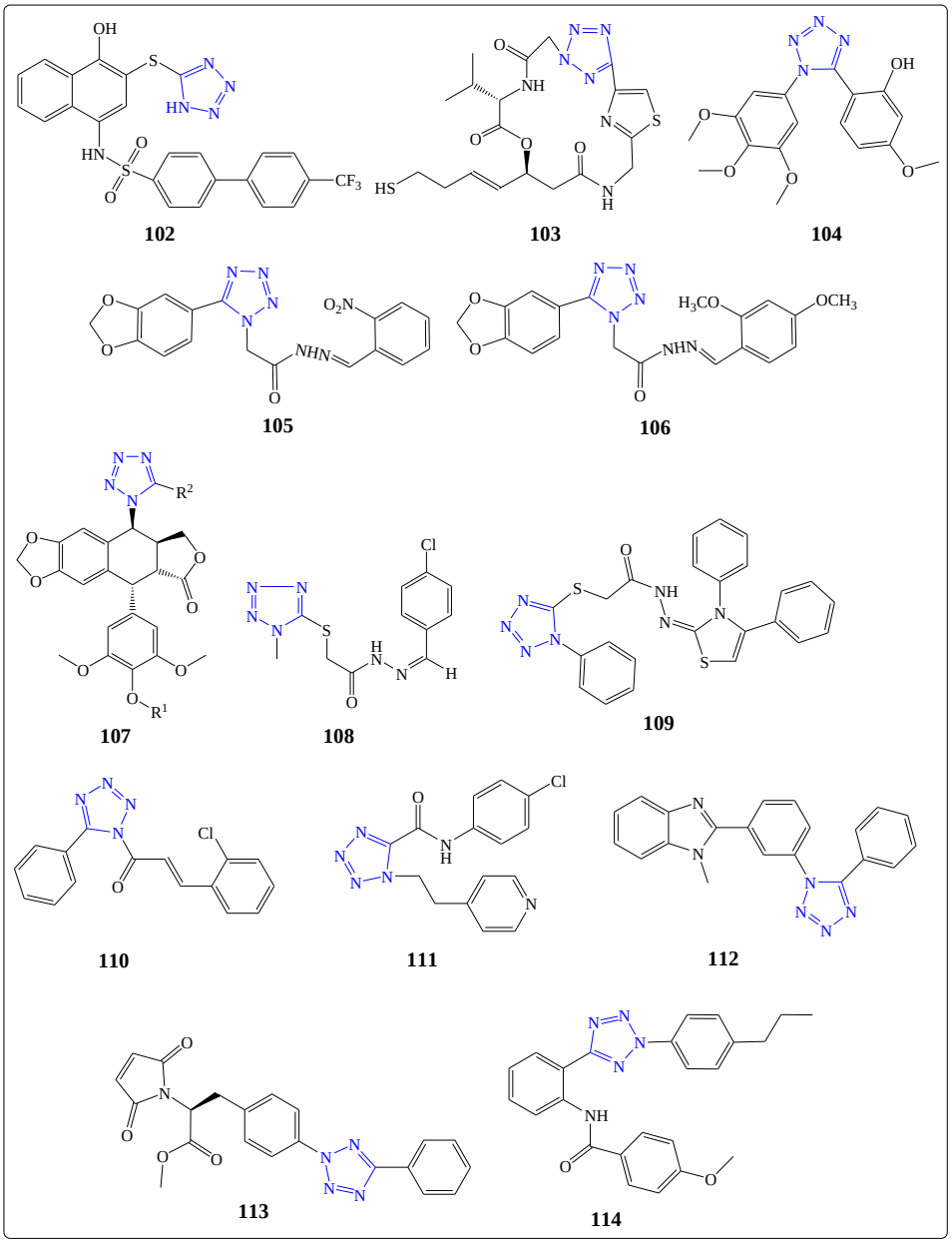


Fig. 1.22: Anticancer activity of 1, 5-disubstituted tetrazole scaffolds

A series of novel 4b-[(5-substituted)-1, 2, 3, 4-tetrazolyl] podophyllotoxin derivatives **(107)** were synthesized *by Hyder I. et al.*[111] All the derivatives were evaluated for their cytotoxicity against a panel of four human cancer cell lines and their IC_{50} values were found to

be in the range of 2.4–29.06 µM. The cell cycle analysis showed that the novel 4b-[(5-substituted)-1, 2, 3, 4-tetrazolyl] podophyllotoxins resulted in cell cycle arrest at G2/M phase and were also found to be the potent inhibitors of tubulin polymerization *in vitro*.

Altıntop M.D. et al[112] have reported the synthesis of a new series of hydrazone derivatives containing tetrazole moiety and investigated their anticandidal activity using umuC and Ames assays to determine genotoxicity of the most effective anticandidal compounds. Among these compounds, compound **(108)** can be considered as the most promising anticancer agent for further investigation owing to its inhibitory effect on A549 cancer cell lines and low toxicity to NIH3T3 cells.

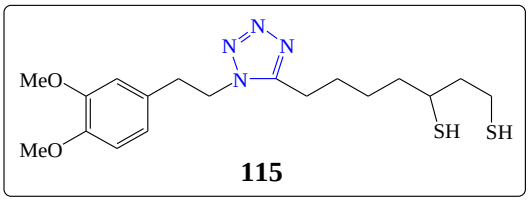
Altıntop M. D. et al[113] have described the synthesis of thiazoline derivatives bearing a hydrazone moiety along with tetrazole ring and evaluated for their antibacterial activity against P. aeruginosa. Furthermore these compounds were also screened for anticandidal activity against C. albicans and antifungal activity against T. harzianum, A. ochraceus, F. solani, F. Moniliforme, F. culmorum. The most effective derivatives were also evaluated for their cytotoxicity against C6 rat glioma cells. The compound **(109)** bearing 1-phenyl-1H-tetrazole was the most promising anticancer agent against C6 glioma cell lines with an IC50 value of 8.3 +- 2.6 µg/ml when compared with cisplatin (IC50 = 13.7 +- 1.2 µg/ml). The synthesis of 5-phenyl tetrazole chalcones were reported by Bhaskar *et al.*[114] The synthesized chalcones were screened and evaluated for their anticancer activity for testing against a panel of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types. The most efficient anticancer compound **(110)** was found to be active with selective influence on ovarian cancer cell lines. *A. Kiselyov S. et al*[115] have developed a series of novel potent tetrazole-5-carboxamide derivatives **(111)** active against VEGFR -2 and -1. These analogues are potentially useful in the treatment of cancer.

Jafar Ahamed A. et al[116] have reported the synthesis of novel benzimidazole derivatives 1-methyl-2-(3-(5-phenyl-1*H*-tetrazol-1-yl)phenyl)-1*H*-benzo[*d*]imidazole **(112)** and evaluated their anticancer, antidiabetic, anti tumor and anti asthmatic properties. *Zhu B. et al*[117] have developed two types of novel chemical tools for the study of DNMT1s- an small molecule, activity-based probe (T1) and twelve tetrazole-derived tryptophan analogs **(113)**, small molecule covalent inhibitors (Gn; n = 1–12). Among these compounds, one of them (G6) possessed reasonable inhibitory activity against DNMT1 in both in vitro enzymatic assays and cell growth proliferation experiments. Both T1 and G6 showed effective labeling of endogenous DNMT1 from mammalian cells by using in vitro competitive pull-down and live-cell bioimaging experiments. *Kohler S.C. et al*[118] have synthesized 21 derivatives of the third-generation P-gp inhibitor HM30181 **(114)**. The compounds were tested for their inhibitory activities against the

BCRP and screened against P-gp (ABCB1) and MRP1 (ABCC1) to confirm the selectivity toward BCRP.

2.6.18. Neuroprotective Activity.

Koufaki M. et al[119] have designed and synthesized new analogues **(115)** containing 1, 2-dithiolane-3-alkyl and protected or free catechol moieties connected through tetrazole in order to explore the influence of the bioisosteric replacement of the amide group on the neuroprotective activity of the lipoic acid/dopamine conjugate. Evaluation of the activity of the new compounds, using glutamate-challenged hippocampal HT22 cells, showed that incorporation of heteroaromatic rings in the alkyl-1, 2-dithiolane moieties in conjunction with another antioxidant, in this case catechol, may result in strong neuroprotective activity.



115

Fig. 1.23: Neuroprotective activity of 1, 5-disubstituted tetrazole scaffolds.

2.6.19. Human Growth Hormone Secretagogue.

A tetrazole-based peptidomimetic 4-(Hydroxybutyl)carbamic acid 2-{5-[1-(2-Amino-2-methylpropionylamino)-2-benzyloxyethyl]tetrazol-1-yl}ethyl Ester (BMS-317180) was discovered as a GHS by *Li J. et al*.[120a] Compound 2 is a potent, novel, orally effective GHS that shows an excellent safety profile in preclinical studies. The safety profile and acceptable pharmacokinetic properties of **(116)** were suitable for long-term efficacy evaluation studies for the prevention of frailty and treatment for cancer cachexia as well as wasting syndrome, and as a result, the compound was advanced for clinical evaluation. Furthermore, *Li J. et al*[120b] have synthesized a series of ortho-substituted compounds and evaluated for the SAR studies of the O-benzyl serine side chain with improved in-vitro and in-vivo activity. Among them, the biphenyl compound **(117)** shows twofold improvement in potency compared to its parent compound BMS-317180. *Li J.J. et al*[121] have synthesized a novel series of N1 substituted tetrazole amides and showed to be potent GHS. Among them, hydroxyl containing analog **(118)** displayed excellent in vivo activity by increasing plasma GH 10-fold in an anesthetized IV rat model.

Hernandez A.S. et al[122a] have discovered a novel class of GHS based on a tetrazole template. In vitro SAR and in vivo potency within this new class of GHS were described. The tetrazole **(119)** exhibits good oral bioavailability in rats and dogs as well as efficacy following an oral 10 mg/kg dose in dogs. In continuation of their work, *Hernandez A.S. et al*[122b] have developed an enantiospecific route for the synthesis of nitriles **(120**. The potency of nitrile 1 has been optimized by introducing 2-arylethyl moiety which provides an additional interaction with the GHS receptor.

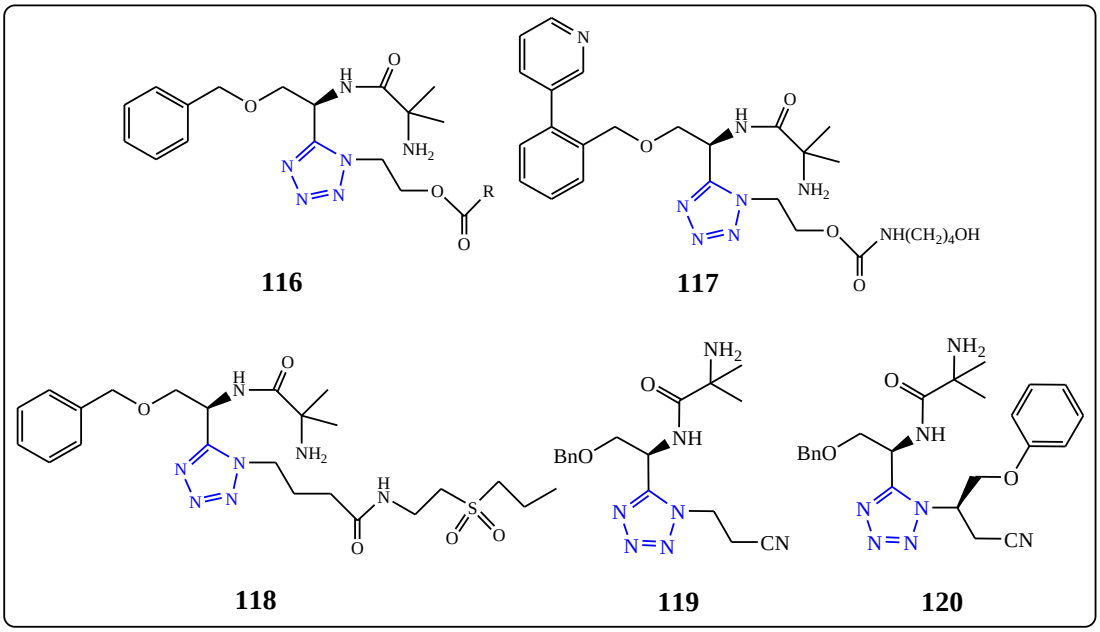


Fig. 1.24: 1, 5-disubstituted tetrazole scaffolds as GHS.

2.6.20. Antiamoebic Activity.

Amoebiasis, a protozoal disease stands as a major health issue in developing countries, affecting hundreds of millions of people around the world. *Wani M.Y. et al.*[123] have reported the synthesis of some novel Sulfonamide derivatives of tetrazole and triazine and investigate their probable antiamoebic effects. They mentioned that none of the tetrazole ring bearing derivatives **(121)** showed any significant activity (IC_{50} = 3.75-7.56 µM) against the test organism where as all the triazine ring bearing derivatives showed moderate to excellent activity (IC_{50} = 1.02-2.85 µM). Furthermore, *Wani M.Y. et al.*[124] have reported the synthesis of some novel tetrazole embedded pyrazoline derivatives and were screened in vitro, to find out effect on the growth of HM1: IMSS strain of *Entamoeba histolytica* to investigate their probable antiamoebic effect. Target compounds were obtained in four-step reaction process in which the compound **(122)** showed excellent antiamoebic activity with IC_{50} value of 0.86 µM.

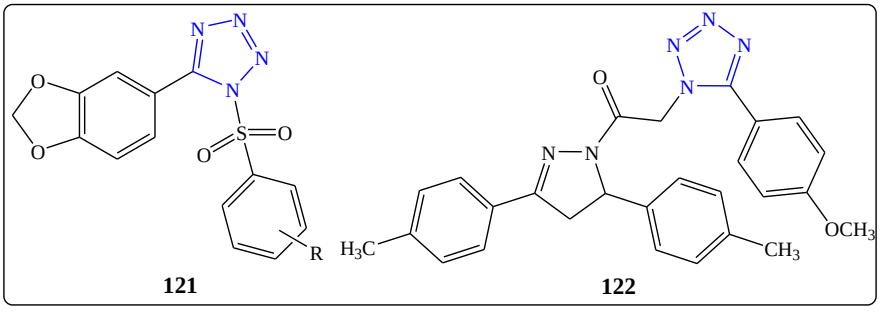


Fig. 1.25: 1, 5-disubstituted tetrazole scaffolds as antiamoebic agents

2.6.21. Antiprotozoal activity

Pandey et al[125] have designed and synthesized some tetrazole embedded chloroquine (CQ) derivatives joined through variable linkers. Interestingly, compounds **123a** and **123b**

showed promising *in vitro* activity against both CQ-S as well as CQ-R strain of *P. falciparum* and also excellent *in vivo* antimalarial activity against *P. yoelli. Cano P. A. et al*[126] have reported the synthesis of novel 3-tetrazolylmethyl-4H-chromen-4-ones (**124)** via an Ugi-azide multicomponent reaction and evaluated for antiprotozoal activity against Entamoeba histolytica, Giardia lamblia and Trichomona vaginalis.

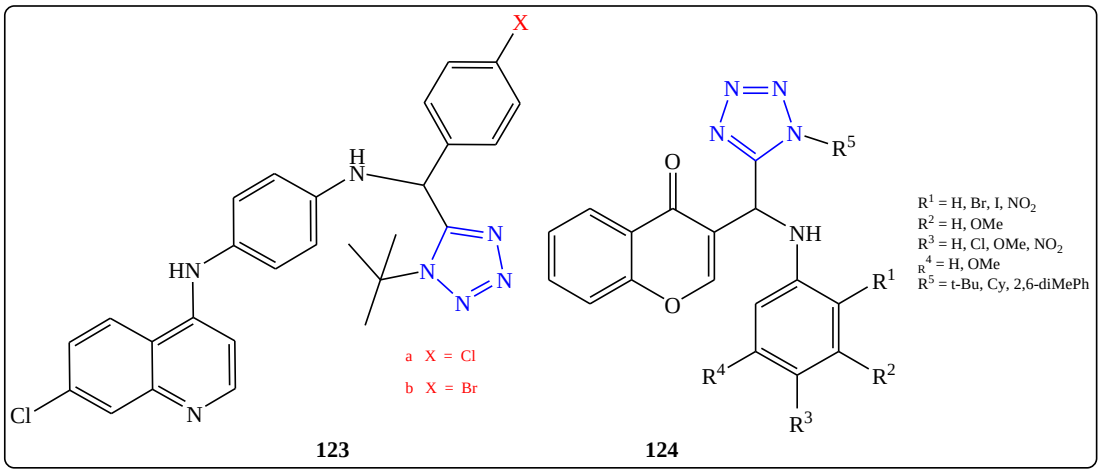


Fig. 1.26: Antimalarial activity of 1, 5-disubstituted tetrazole scaffolds.

2.6.22. Miscellaneous biological activities.

Ortar et al[127] have reported a new series of 1, 5-disubstituted tetrazoles **(125)** and evaluated as inhibitors of anandamide cellular uptake. Some of them inhibit the uptake process with a relatively high potency (IC_{50} = 2.3–5.1 µM) and selectively over other proteins involved in endocannabinoid action and metabolism. *O'Brien P.M. et al*[128] have examined the structure-activity relationship for a series of retroamide tetrazole derivatives where they found that, the length of the tetrazole side chain was crucial than its position for potent ACAT inhibition. Of the substituents evaluated on the benzamide ring, the 3-nitro derivative **(126)**, provided optimal activity in vitro, but the 2, 6-dimethyl substituted compound **(127)**, was considerably more efficacious in vivo, in the cholesterol-fed rat model.

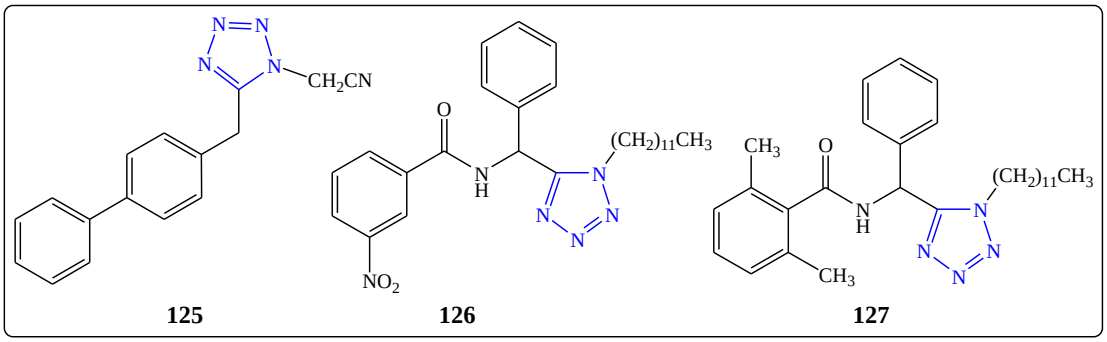


Fig. 1.27 Other bioactive 1, 5-disubstituted tetrazole scaffolds

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CHAPTER 2

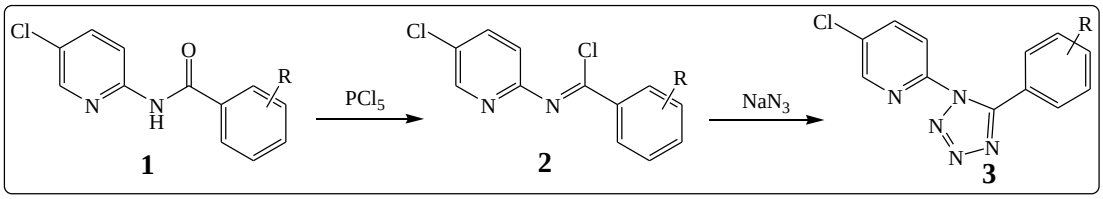
SYNTHESIS OF 1, 5-DISUBSTITUTED TETRAZOLES FROM SECONDARY AMIDES USING TITANIUM TETRACHLORIDE ($TiCl_4$)

The chemistry of tetrazoles has acquired enormous importance in recent years due to its isosteric nature with carbonyl group. The 1, 5-disubstituted tetrazoles were incorporated into longer peptides as isosteres for the cis-amide bond.[1] The replacement of the cis-amide group by 1, 5-disubstituted tetrazole enhances the metabolic stability of the molecule and shows a close similarity in acidic character with carboxylic acid group. This inspired the medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents. The 1, 5-disubstituted tetrazole moieties were found in numerous biologically active substances, some of these scaffolds were well described in Chapter-1.

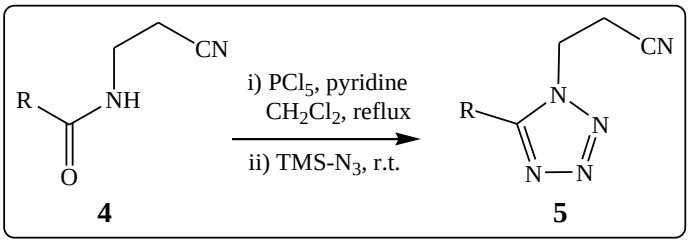
2.2 Literature Survey

The synthesis of 1, 5-disubstituted tetrazole is well described in literature. It can be synthesized from amides, [2] thioamides, [3] imidoyl chlorides, [4] imidoyl benzotriazoles, [5] oximes, [6] isocyanates,[7] etc. Out of these, the secondary amides are easily available or can be easily prepared from amines, so the interest has been created towards the use of amides in the synthesis of 1, 5-disubstituted tetrazoles. The several methods have been reported for the conversion of secondary amides to the corresponding 1, 5-disubstituted tetrazoles.

P. Shanmugapandiyan et al[8] have reported the synthesis of 5-chloro-2-(5-substituted phenyl-1*H*-tetrazol-1-yl)pyridine **(3)** in a two step reaction from secondary amide **(1)** where secondaryamide was first converted to imidoyl chloride **(2)** followed by cycloaddition of N-Pyridyl-2-yl imidoformylchloride-benzene with sodium azide under mild conditions.



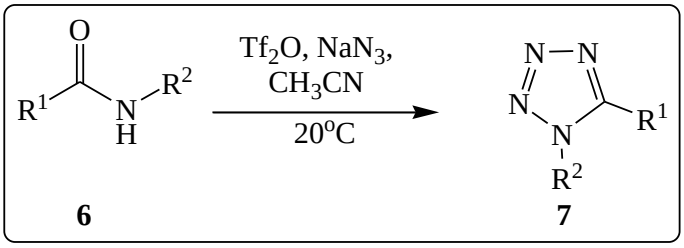
Scheme 2.1: Synthesis of 1, 5-disubstituted tetrazole via imidoyl chloride



Scheme 2.2: Synthesis of cyanoethyl-protected tetrazoles

Kennedy L.J.[2] has reported a mild and general one-pot procedure for the conversion of cyanoethyl amides **(4)** to cyanoethyl-protected tetrazoles **(5)** with TMS-N_3 via the intermediacy of imidoyl chlorides generated in situ with phosphorus pentachloride. This synthetic route works well with sterically hindered amides and is compatible with acid sensitive functionality.

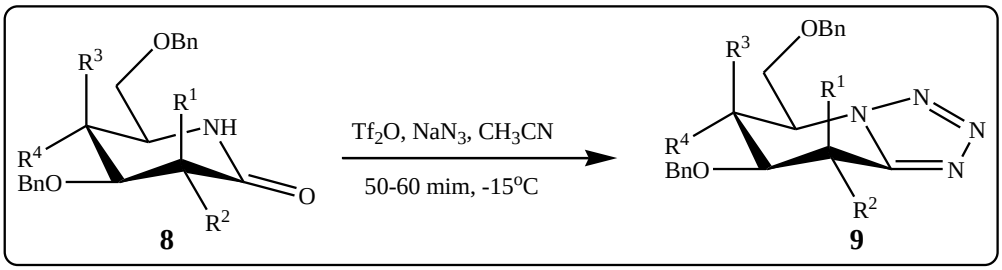
In 1993, *Thomas E.W.*[9] has introduced trifluoromethanesulfonic anhydride (Tf_2O) for the conversion of secondary amides **(6)** to 1, 5-disubstituted tetrazoles **(7)** using NaN_3 in a mild reaction conditions.



6 **7**

Scheme 2.3: Tf_2O induced synthesis of 1, 5-disubstituted tetrazoles

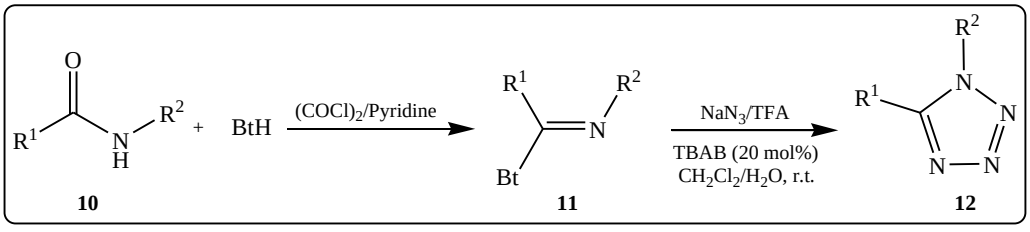
A classical and the high yielding transformation of glyconolactams **(8)** into the corresponding tetrazoles **(9)** using trifluoromethanesulfonic anhydride (Tf_2O) and sodium azide in acetonitrile have been described by *Vonhoff S. et al.*[10]



8 **9**

Scheme 2.4: Synthesis of tetrazoles from glyconolactams

Further Katritzky A. R. *et al*[5] have reported the synthesis of 1, 5-disubstituted tetrazole from readily available amides, with the formation of imidoylbenzotriazole as an intermediate. The imidoylbenzotriazole on treatment with NaN_3 in aqueous solution, where the protocol required 1 eq. TFA and 0.2 eq. TBAB in a (1:1) mixture of H_2O/CH_2Cl_2, gives 1, 5-disubstituted tetrazole.

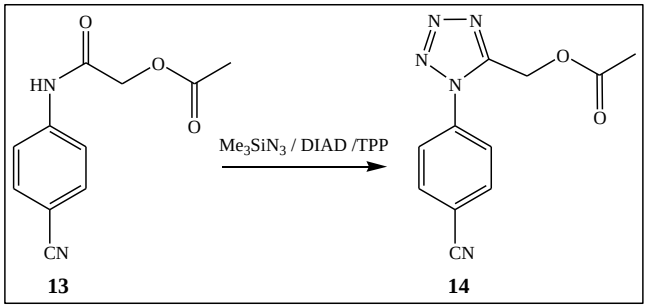


10 **11** **12**

Scheme 2.5: Synthesis of 1, 5-disubstituted tetrazoles via imidoyl brnzotriazoles

In the synthesis of a series of novel 4-(5-substituted amino methyl)-*1H*-tetrazol-1-yl)benzonitriles, *Venkatanarsimha Rao et al*[11] have prepared 1, 5-disubstituted tetrazole **(14)** as

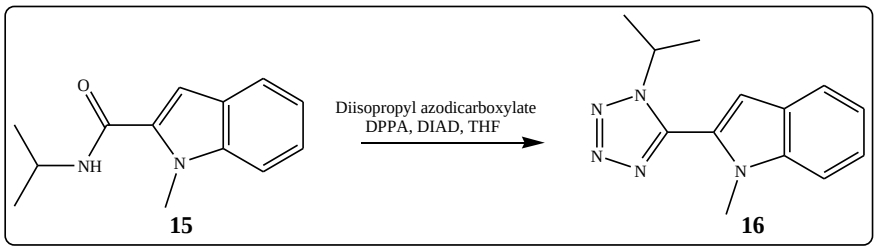
an intermediate from secondary amide **(13)** using CH_3SiN_3 in DIAD/TPP conditions to form the 1-(4-cyanophenyl)-*1H*-tetrazol-5-yl) methyl acetate.



13 **14**

Scheme 2.6: Synthesis of 1, 5-disubstituted tetrazoles using DIAD/TPP

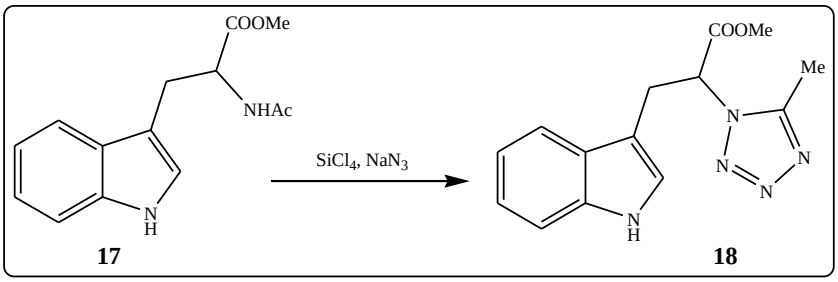
Schroeder G. M. et al[12] have described improved reaction conditions for converting sterically hindered amides **(15)** to their corresponding 1, 5-disubstituted tetrazoles **(16)** by reacting amides with diisopropylazo dicarboxylate in presence of diphenyl-2-pyridyl phosphine in THF. These reaction conditions have successfully applied to generate biologically active 1, 5-disubstituted tetrazoles as *cis*-amide bond surrogates.



15 **16**

Scheme 2.7: Synthesis of 1, 5-disubstituted tetrazoles from sterically hindered amides

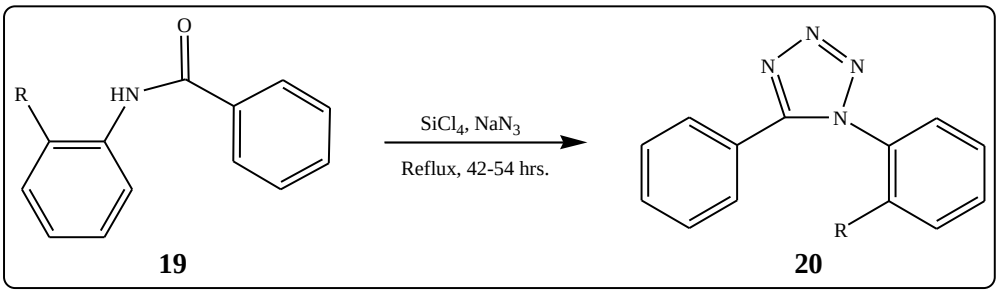
Tetrazole containing amino acid derivatives were prepared through the reaction of TCS-NaN_3 reagent with *N*-acetyl-amino acid esters.[13] In continuation of the work, the tryptophane derivatives having a tetrazole fragment can be prepared from accessible *N*- acyl-(*R, S*)-tryptophane esters by the action of tetrachlorosilane–sodium azide. By heating *N*-acetyl-(*R, S*)-tryptophane methyl ester **(17)** with tetrachlorosilane and sodium azide in boiling acetonitrile obtained *α*-substituted methyl 5-methyl-1-tetrazolylacetate **(18)**.[14]



17 **18**

Scheme 2.8: Synthesis of 1, 5-disubstituted tetrazoles using $SiCl_4$

Recently, by using the procedure reported by *Esikov et al*, *Najafi P. et al*[15]showed that tetrachlorosilane-sodium azide system can be used for the conversion of bulky secondary N-benzoyl amides **(19)** to sterically hindered 1, 5-disubstitutedtetrazoles **(20)** in good yields.

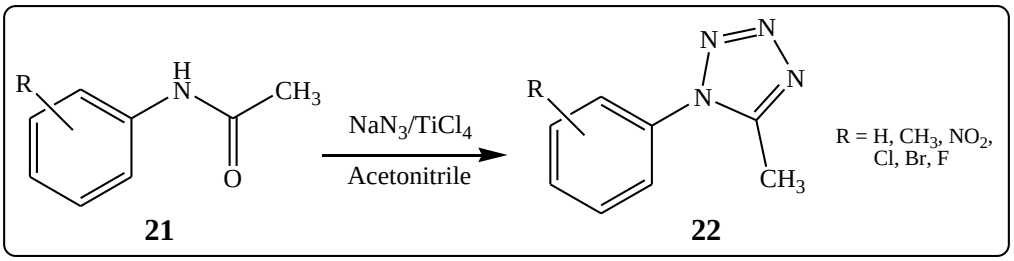


19 **20**

Scheme 2.9: Synthesis of 1, 5-disubstituted tetrazoles from sterically hindered amides

2.3 Present Work

In view of the above mentioned problems and the need for the simple and industrially viable procedure for the synthesis of 1, 5-disubstituted tetrazoles, theapproach has been made to use titanium tetrachloride ($TiCl_4$) for the conversion of secondary amides **(21)** to 1, 5-disubstituted tetrazoles **(22)** using NaN_3 in acetonitrile.



21 **22**

Scheme 2.10: Synthesis of 1, 5-disubstituted tetrazoles using $TiCl_4$

2.4 Result and Discussion

The secondary amides were prepared from commercially available substituted aniline according to the method described in the literature. The reaction of secondary amides (**21**) and NaN_3 was carried out using $TiCl_4$ in acetonitrile that led to the formation of 1, 5-disubstituted tetrazoles (**22**) in 90% yield. With this encouraging result, next to evaluate the solvent effect, we investigated the reaction under similar conditions using various solvents and the results are summarized in Table **2.1**.

Table 2.1: Synthesis of 1, 5-disubstituted tetrazoles in different solvents

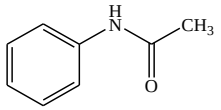
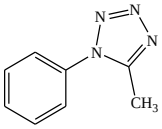
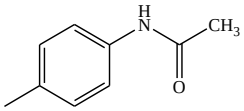
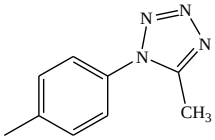
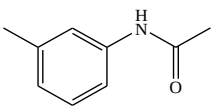
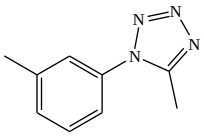
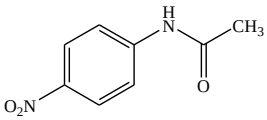
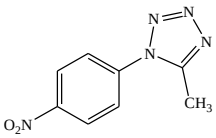
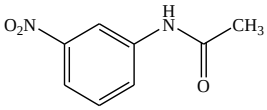
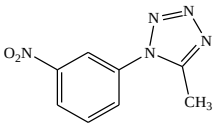
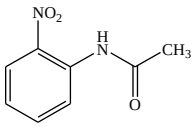
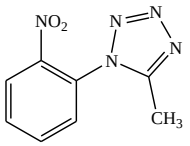
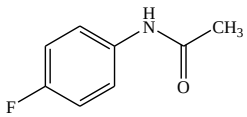
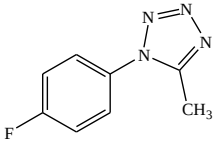
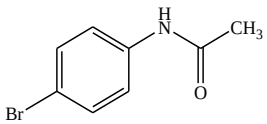
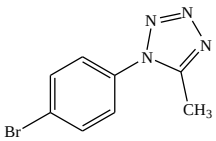
Entry[a]	Solvent	Time (hrs)	Yield (%)[b]
1	Benzene	24	---
2	CH_2Cl_2	24	30
3	DMSO	24	50
4	Acetonitrile	8	87

[a]Amide(1eq.), azide(1.5eq.), $TiCl_4$(2eq.), Solvents(10vol), atrefluxcondition, [b]Isolated yield

In benzene as solvent, the reaction did not proceed whereas in CH_2Cl_2 only 26% and in DMSO only 45% of the product was formed while refluxing the reaction mixture for 24 hrs. After substantial experimentation with different solvents, acetonitrile was found to be superior to

the other solvents. We next, investigated the amount of $TiCl_4$ required to catalyze the transformation. As less as 1 eq. of $TiCl_4$ afforded the products in 60% yield after 12 hr. By using 1.5 eq. of $TiCl_4$, the product yields were improved to 75%, the reaction time almost remained the same as that with 1 eq. On the other hand, using 2 eq. of $TiCl_4$ as a catalyst the reaction afforded 90% yield in 8 h. This reveals that using 2 eq. of $TiCl_4$ as a catalyst afforded higher yield and lower reaction time as well.aromatic compounds bearing substituents such as $–CH_3$, -OMe, -Cl, -Br, and - NO_2 on phenyl ring give the corresponding 1, 5-disubstituted tetrazoles in good to excellent yields **(Table 2.2)**.

Table 2.2: Synthesis of 1, 5-disubstituted tetrazoles

Entry	Substrate	Product	Time	Yield (%)
22a			8	87
22b			9	85
22c			9	83
22d			6	93
22e			6.5	90
22f			9	89
22g			6	92
22h			7	91

The secondary amides having substitution at *para*- position gives high yields and takes less reaction time when compared with *meta*- and *ortho*- phenyl substituted secondary amides.

Table 2.3 illustrates the IR data of C=N stretching frequencies of 1, 5- disubstituted tetrazole derivatives **(22a-h)** synthesized in the present work. From thetable, it is evident that all the newly synthesized tetrazole compounds give the absorption band in the range 1590-1630 cm^{-1} for C=N functional group in the tetrazole ring. The IR spectral values obtained for 1, 5-disubstituted tetrazoles in the present work are in agreement with the values reported in literature.[16]

Table 2.3: C=N and N=N stretching frequencies of 1, 5-disubstituted tetrazoles

Compounds	C=N, Frequency(cm^{-1})	N=N, Frequency(cm^{-1})
22a	1593	1498
22b	1631	1496
22c	1607	1492
22d	1610	1485
22e	1614	1496
22f	1608	1496
22g	1600	1514
22h	1627	1492

The absorption bands for N=N functional group in the newly synthesized 1, 5-disubstituted tetrazoles **(22a-h)** are presented in the **Table 2.3**.

From the **Table 2.3**, it is inferred that all the newly synthesized compounds showed an absorption band around 1400 cm-1, which confirms the presence of N=N functional group. An absorption band around 1500 cm^{-1} showed the presence of N=N group of tetrazole ring. These values are in agreement with the values reported in literature.[17]

The appearance of anabsorption band around 1250-1300 cm^{-1} reveals that there is N-N=N linkage present in a molecule shown in **Table 2.4**. In the present work, similar observations are found with regard to the presence N-N=N linkage of tetrazole ring. The IR absorptions at 1290 cm^{-1}, 1292 cm^{-1}, 1288 cm^{-1}, 1298 cm^{-1}, 1288 cm^{-1}, 1274 cm^{-1}, and 1273 cm^{-1} are due to the presence of N-N=N functional groups present in the compounds **(22a-h)** respectively. **Table 2.4** presents the data of tetrazole ring frequencies of the newly synthesized compounds **(22a-h)**.

These values are also in accordance with the values of tetrazole ring reported in litetrature.[18] The presence of C-Br linkage in the compound **22h** is confirmed by the presence of an absorption band at 672 cm^{-1}.

Table 2.4: N-N=N and tetrazole ring frequencies of 1, 5-disubstituted tetrazoles

Compounds	Characteristic Absorption Frequencies (cm^{-1})	
	N-N=N	Tetrazole Ring
22a	1290	1080, 1116
22b	1292	1082, 1118
22c	1295	1092, 1123
22d	1288	1095, 1116
22e	1298	1080, 1109
22f	1288	1089, 1112
22g	1274	1041, 1093
22h	1295	1092, 1123

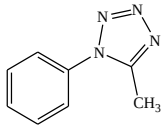
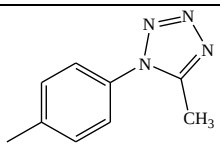
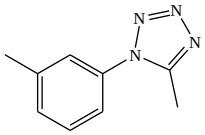
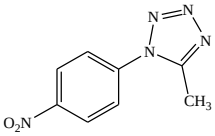
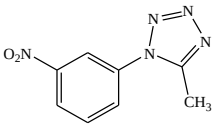
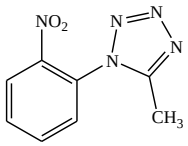
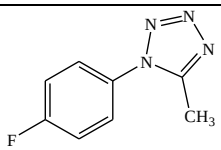
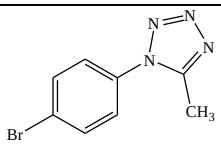
Furthermore, the evidence for the formation of the substituted 1, 5-disubstituted tetrazoles **(22a-h)** were obtained from the ^{1}H NMR and ^{13}C NMR spectra which provedto be the diagnostic tool for the positional elucidation of the proton and carbon atoms respectively.[19] **Table 2.5** given below presents the data of chemical shifts of proton in the ^{1}H NMR spectra of 1, 5-disubstituted tetrazoles.

A significant fact of the data given in **Table 2.5** indicates that the aromatic protons were found in the range of δ 7.5–8.5. The aromatic protons *ortho* to the tetrazole ring in compound **22b** are found at δ 7.34 whereas the protons *ortho* to the methyl group were found at δ 6.94. This indicates that the benzene protons *ortho* to the tetrazole ring are deshielded by δ 0.16 ppm relative to the protons *ortho* to methyl group. The deshielding effect may be attributed to the presence of methyl group in the first position of tetrazole ring. The deshielding effect increases when methyl group get replaced by nitro group **22c.** In ^{1}H NMR spectrum of compound **22c**, the aromatic protons *ortho* tothe tetrazole ring are found at δ 8.17 whereas the protons ortho to the nitro group observed at δ 8.24. Due to the presence of electron withdrawing nitro group, the protons of the benzene ring *ortho* to the nitro group are deshielded by δ 0.07 ppm relative to the protons *ortho* to tetrazole ring. The deshielding effect may be attributed due the presence of methyl group in the first position of tetrazole ring and nitro group as well.

The analogous observations are found for the other synthesized compounds. Hence, the ^{1}H-NMR spectra of the synthesized compounds lend convincing evidence to the assigned structure. Similar type of observations was reported previously for the tetrazole containing aromatic compounds.[20]

All of the above observations reveal the presence of 1, 5-disubstituted tetrazole moiety present in the newly synthesized compounds.

Table 2.5: 1H-NMR chemical shifts of 1, 5-disubstituted tetrazoles

Entry	Compounds	Chemical shifts (δppm)		
		H(Ar)	-CH_3 (Ar)(s)	-CH_3 (tetrazole)(s)
22a		7.48(s, 5H)	---	2.38
22b		7.32-7.35(m, 4H).	2.41	2.28
22c		7.33-7.36(m, 4H).	2.38	2.26
22d		8.17(d, 2H), 8.24(d, 2H).	---	2.89
22e		8.45-8.48(m, 1H), 8.39-8.42(m, 1H), 8.10-8.12(m, 1H), 7.80-7.82(m, 1H)	---	2.49(s, 3H)
22f		8.40-8.42(m, 1H), 8.20-8.23(m, 1H), 7.91-293(m, 1H), 7.75-7.77(m, 1H).	---	2.15(s, 3H)
22g		7.65(d, 2H), 7.39(d, 2H).	---	2.42(s, 3H).
22h		7.75(d, 2H), 7.58(d, 2H).	---	2.45(s, 3H).

2.5 Experimental

All the secondary amides were synthesized in our laboratory where as other chemicals were purchased from commercial suppliers. Melting points were determined in open capillaries and were uncorrected. The progress of reaction and purity of the product were monitored by thin layer chromatography using precoated Silica 60/UV_{254}(SDFCL). NMR spectra were recorded using a Bruker DRX-300 (300MHz) spectrometer and reported in δppm downfield from TMS as

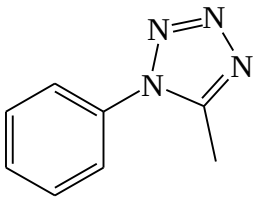
internal standard. FT-IR spectra were recorded on Shimadzu IRAffinity-1S spectrophotometer and are reported in cm^{-1}.

General procedure for the synthesis of 1, 5-disubstituted tetrazoles

To a stirred solution of acetanilide (2gm, 0.5moles) in dry acetonitrile (5ml) at 0- 5ºC, $TiCl_4$ (2.8gm, 1.0moles) was added drop wise with stirring and the mixture was stirred at room temperaturefor30 min. Then Sodium azide(0.93gm, 0.5 mol.)was added to it andthe reaction mixture was heated at 80-90ºC. After 2 hrs the additional amount of sodium azide (0.93gm, 0.5 mol.) was added to reaction mixture and heating was continued for further 4-6 hrs. The reaction was monitored by TLC after 3hrs. Then the reaction mixture was cooled and poured over crushed ice and the product separated out was filtered, washed with water, dried and recrystallized from alcohol.

All the other compounds were synthesized by using same procedure as given above. The synthesized compounds were characterized by IR, ^1H NMR and ^{13}C NMR techniques.

5-METHYL-1-PHENYL-1H-TETRAZOLE (22A)

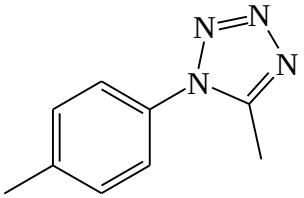


mp:103-105ºC.

^{1}HNMR($CDCl_3$): δ 7.48 (s, 5H), 2.38 (s, 3H).

IR(KBr, cm^{-1}): 3061, 2947, 1593, 1498, 1458, 1411, 1377, 1290, 1170, 1116, 1080, 985, 923, 850, 765, 690.

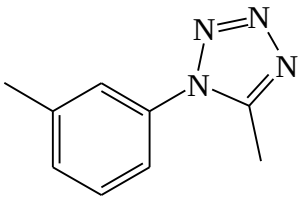
5-METHYL-1-P-TOLYL-1H-TETRAZOLE (22B)



mp:87-89ºC.

^{1}H-NMR ($CDCl_3$): δ 7.32-7.35 (m, 4H), 2.41 (s, 3H), 2.28 (s, 3H). **IR (KBr, cm^{-1})**: 3051, 2931, 2864, 1631, 1585, 1518, 1496, 1462, 1410, 1383, 1292, 1269, 1118, 1082, 1028, 987, 800, 767, 721.

5-METHYL-1-M-TOLYL-1H-TETRAZOLE (22C)



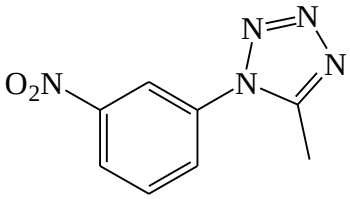
mp: 84-87ºC.

^{1}H-NMR ($CDCl_3$): δ 7.33-7.36 (m, 4H), 2.38 (s, 3H), 2.26 (s, 3H). **IR (KBr, cm^{-1})**: 3059, 2943, 2876, 1607, 1577, 1512, 1492, 1451, 1413, 1387, 1295, 1277, 1123, 1092, 1020, 808, 756, 724.

5-METHYL-1-(3-NITROPHENYL)-1H-TETRAZOLE (22E)

mp:151-153ºC

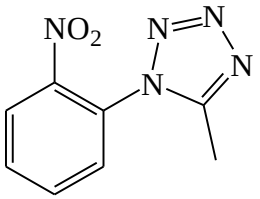
H-NMR ($CDCl_3$): δ 8.45-8.48 (m, 1H), 8.39-8.42 (m, 1H), 8.10-8.12 (m, 1H), 7.80-7.82 (m, 1H), 2.49 (s, 3H)**IR (KBr, cm^{-1})**: 3088, 2977, 1619, 1587, 1516, 1491, 1429, 1344, 1291, 1118, 1099, 1025, 918, 853, 816, 757



5-METHYL-1-(2-NITROPHENYL)-1H-TETRAZOLE(22F)

mp:117-119ºC

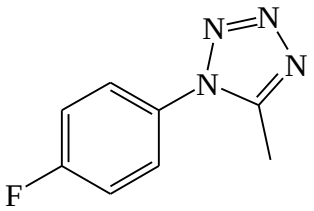
^{1}H-NMR ($CDCl_3$): δ 8.40-8.42 (m, 1H), 8.20-8.23 (m, 1H), 7.91-7.93 (m, 1H), 7.75-7.77 (m, 1H), 2.15(s, 3H). **IR (KBr, cm^{-1})**: 3093, 2989, 1608, 1581, 1527, 1496, 1411, 1344, 1305, 1280, 1257, 1112, 1089, 1024, 987, 854, 750, 723



1-(4-FLUOROPHENYL)-5-METHYL-1H-TETRAZOLE (22G)

mp:81-83ºC

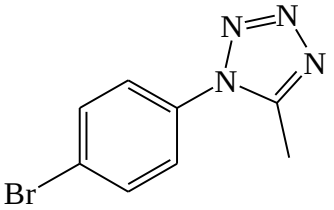
^{1}H-NMR ($CDCl_3$): δ 7.65 (d, 2H), 7.39 (d, 2H), 2.42 (s, 3H) **IR (KBr, cm^{-1})**: 3120, 2983, 1600, 1514, 1411, 1383, 1274, 1230, 1157, 1093, 1041, 989, 839, 690



1-(4-BROMOPHENYL)-5-METHYL-1H-TETRAZOLE (H)

MP:117-119ºC

^{1}H-NMR ($CDCl_3$): δ 7.75 (d, 2H), 7.58 (d, 2H), 2.45 (s, 3H) **IR (KBr, cm^{-1})**: 3084, 2983, 2879, 1627, 1516, 1492, 1408, 1273, 1118, 1101, 1076, 1039, 1008, 844, 821



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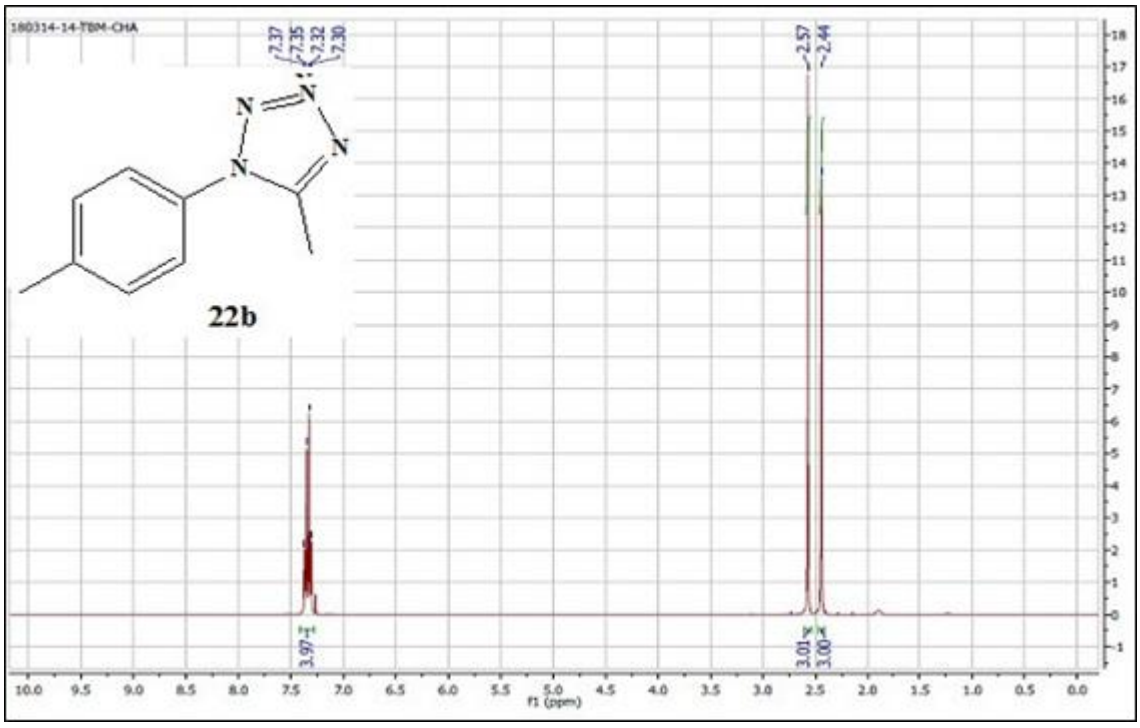

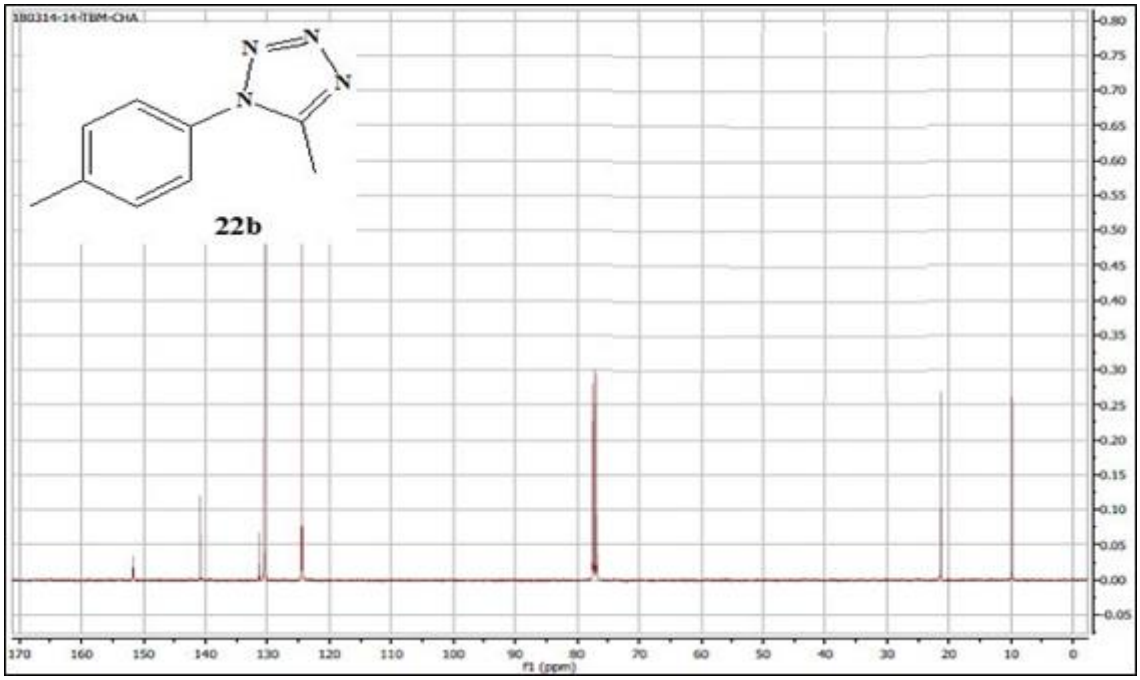

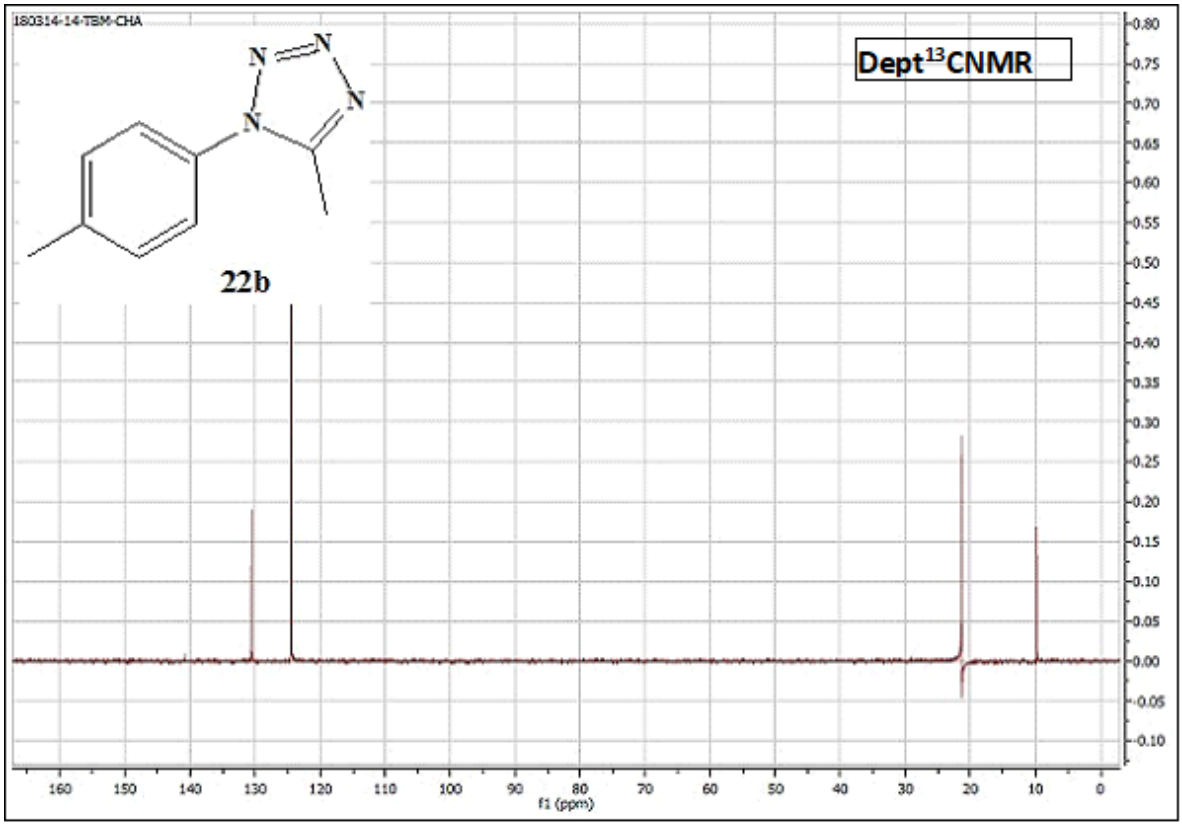
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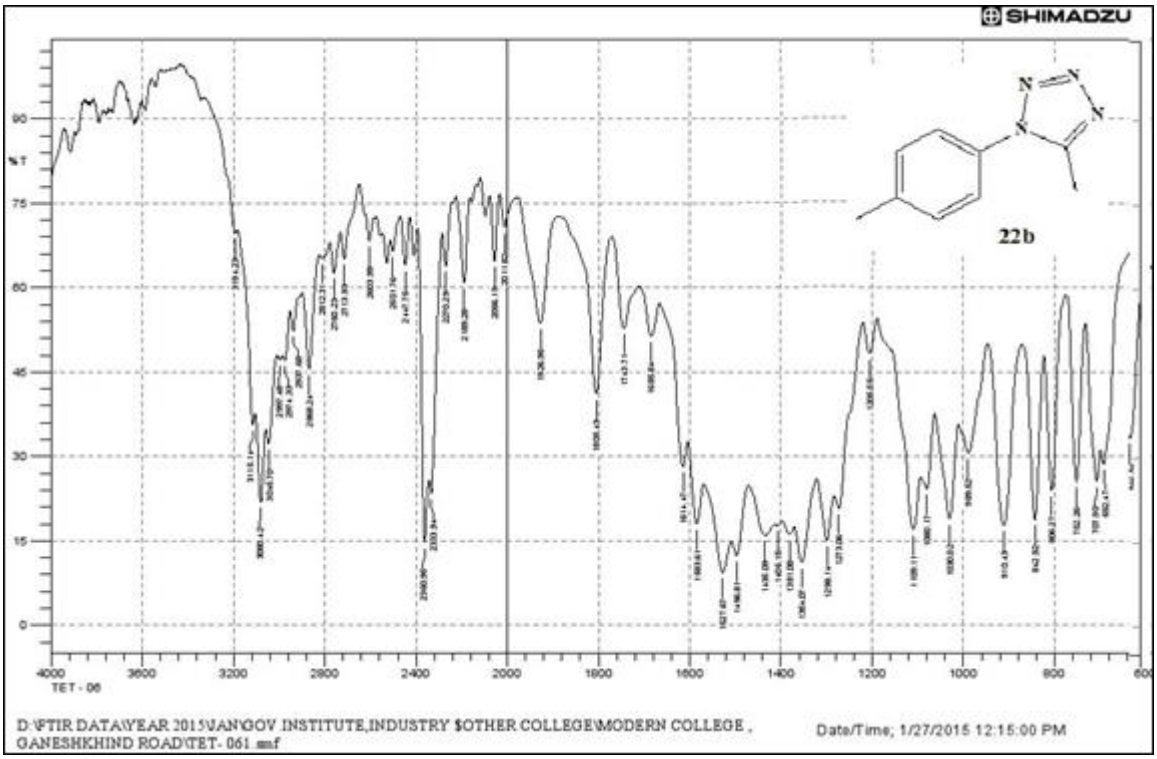
f1 (ppm)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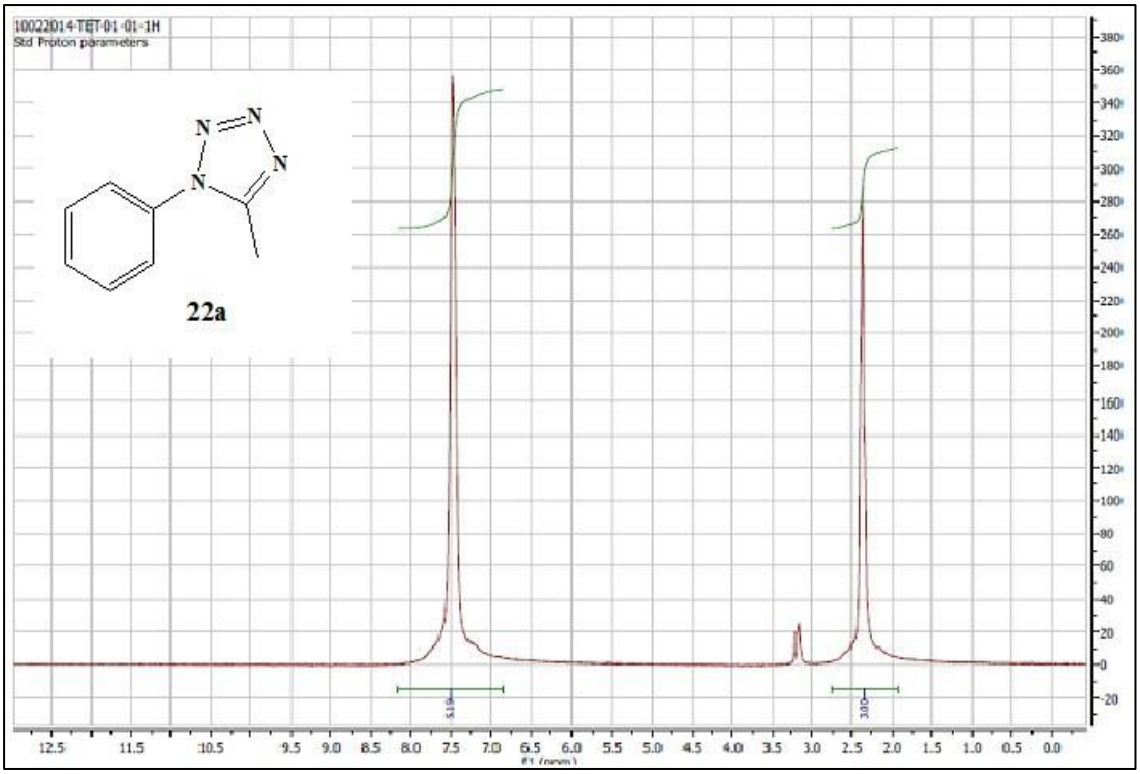
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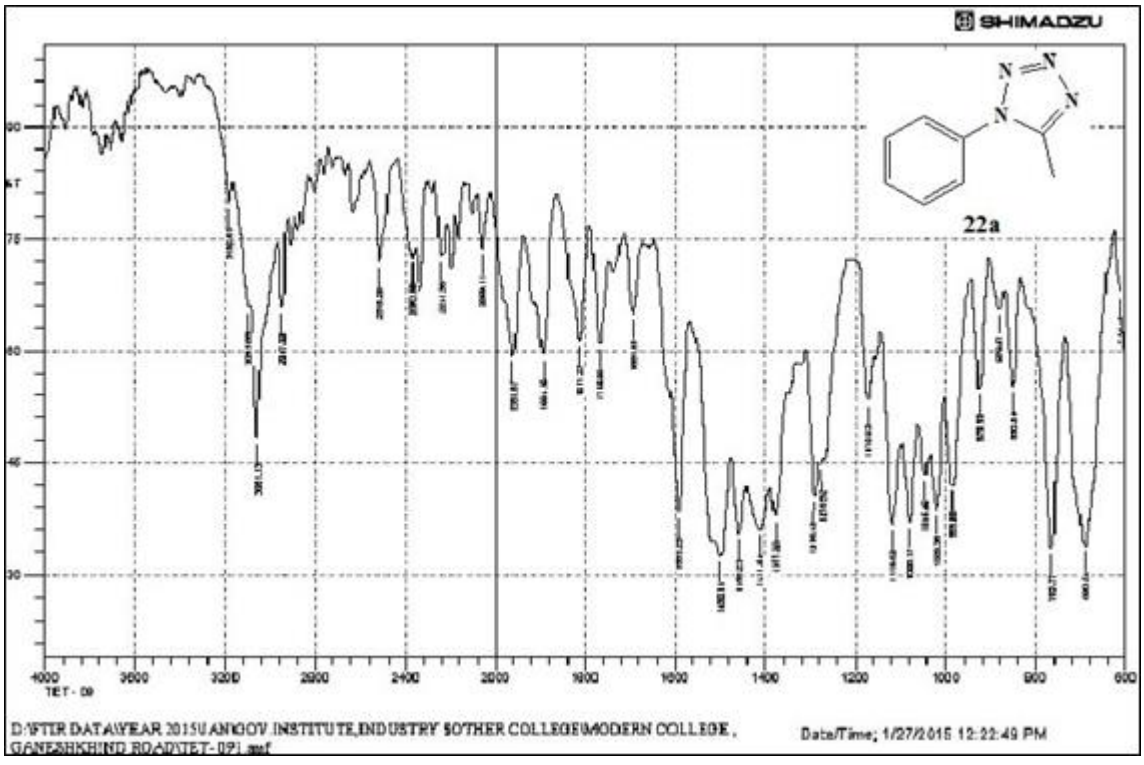
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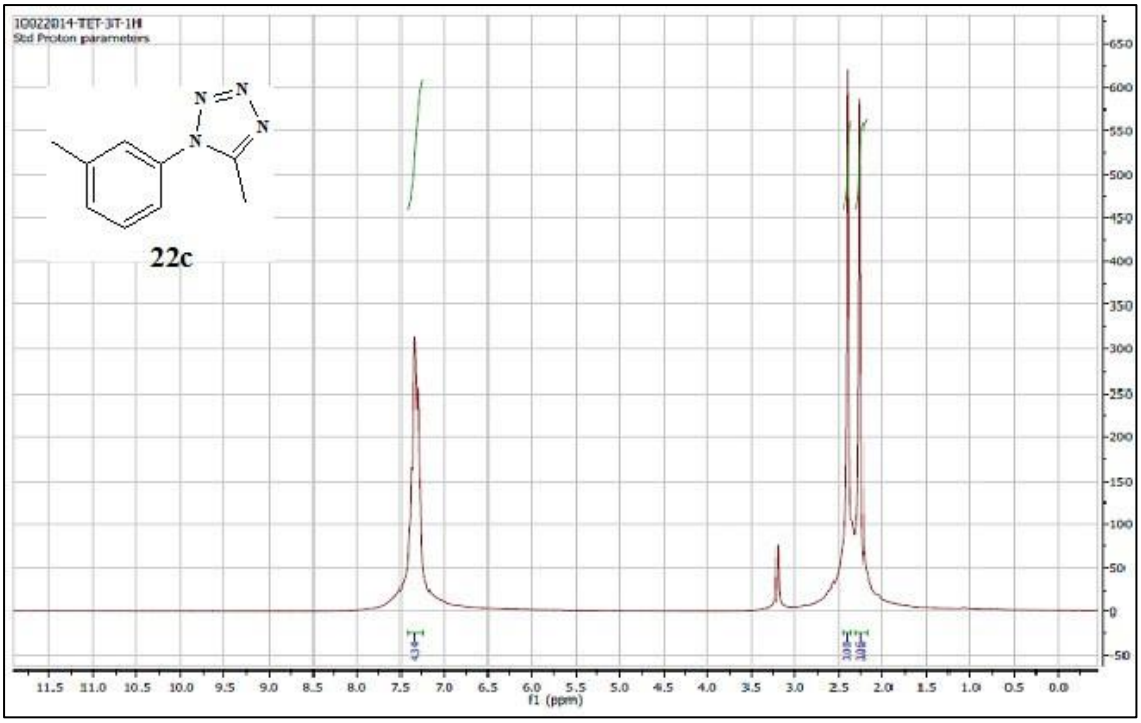
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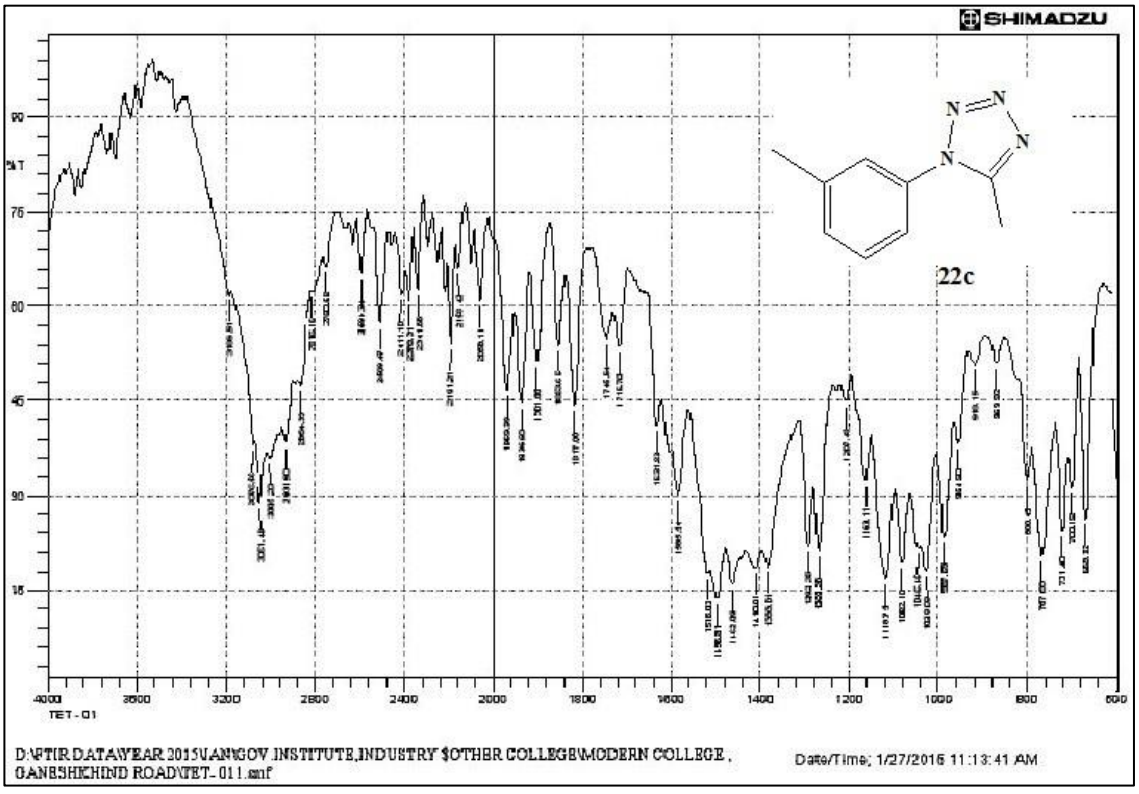
f1 (ppm)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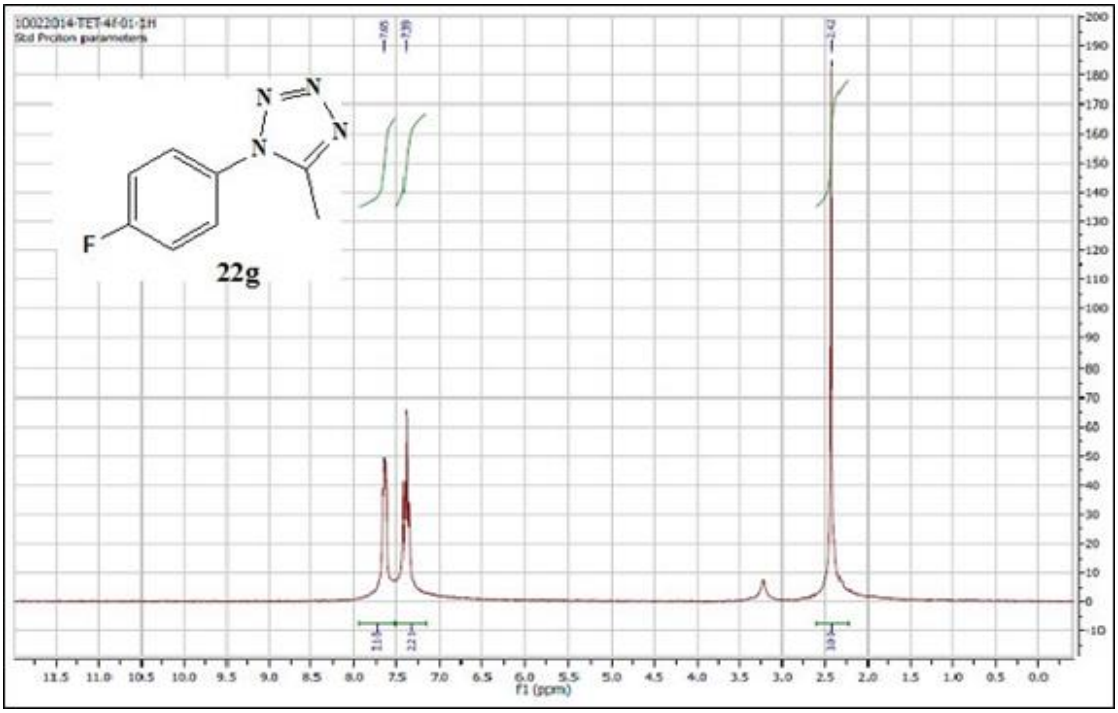

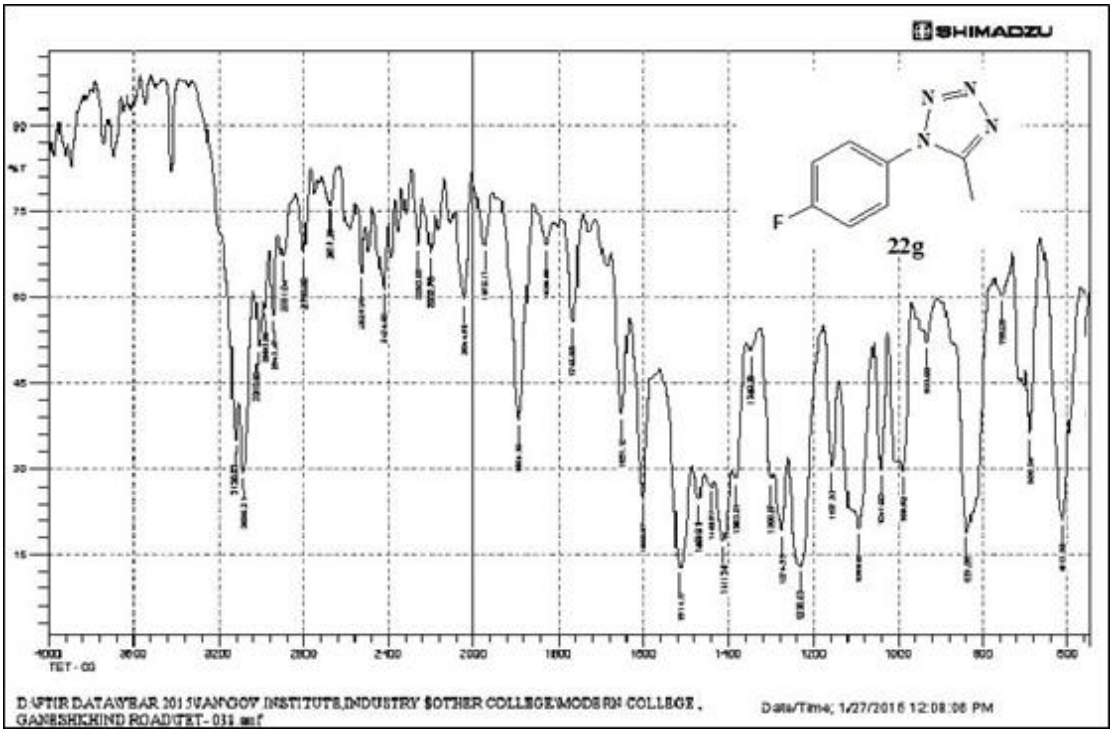

2.7 Conclusion

In conclusion, we have successfully developed a novel protocol for high yielding method for the synthesis of 1, 5 - disubstituted tetrazoles from secondary amides using $TiCl_4$ as a catalyst for first time. The use of $TiCl_4$ enhances the reactivity of inexpensive sodium azide towards secondary amides. The reaction takes less time for the conversion of secondary amides to 1, 5 - disubstituted tetrazole with good to excellent yields when compared with other reported

methods. This methodologymaybe used efficientlyfor the synthesis of variety of 1, 5 - disubstituted tetrazoles.

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[1] Marshall, G. R. In the Chemical Regulation of Biological Mechanisms Ed. Creighton, A. M.; Turner, S. The Royal Society of Chemistry, Burlington House: London, **1982** Vol. 279-292. b) May, B. C. H.; Abell, A. D. *Tetrahedron Lett.*, **2001**, *42*, 5641.

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CHAPTER 3
SYNTHESIS OF SUBSTITUTED (5-METHYL-1*H*-TETRAZOL-1-YL)BENZENAMINES

Introduction

The successive progress in medicinal chemistry continues to highlight the need for practical and efficient routes to generate drug-like compounds.[1] Due to their high degree of atom economy, convergence and productivity, the aromatic amines have been found to provide a promising approach through which drug-like nitrogen heterocycles are efficiently generated.[2]

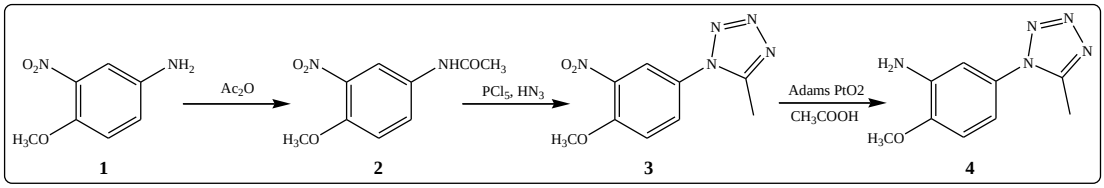
Aromatic amines and their derivatives are important functionalities, used as important starting materials for the manufacture of a variety of chemicals such as dyestuffs, pharmaceuticals, agrochemicals, surfactants, pesticides, polymers, etc.[3] Various natural and synthetic biomolecules are derived by replacing one or more hydrogen atoms of ammonia molecule by alkyl/aryl group(s). Due to its unique biological properties the amine moiety plays a vital role in chemotherapeutics of numerous diseases.[4] In nature, amines occur in proteins, vitamins, alkaloids and hormones. Synthetic examples include polymers, dyestuffs and drugs. Considering their wide range of applications in the fields of medicinal, bioorganic and synthetic organic chemistry, there has been tremendous interest in synthesis of new bioactive amines and developing efficient methods for their derivatives.

3.1 Literature Survey

The derivatives of 1, 5-disubstituted tetrazoles are used as the key organic compounds owing to their synthetic and effective biological activities such as anti- inflammatory, antiviral, antibiotics, anti-ulcer, anti-tubercular, anti-hypertensive etc (Chapter I). In spite of huge focus in the synthesis and creation of new pharmaceutical products of 1, 5-disubstituted tetrazoles, surprisingly, a Sci-Finder® and CrossFire® survey revealed that only two synthetic strategies have been reported with poor chemo selective and low yield synthetic routes. The physicochemical studies of these compounds are not well elaborated in literature.

Herbst R. M. et al[5, 6] have reported a series of phenyl acetamides $RR'C_6H_3NHCOR''$ and corresponding disubstituted tetrazoles $RR'C_6H_3N.N:N.N:CR''$ have been prepared for their pharmacological tests. The nitration of *p*-$MeOC_6H_4NH_2$ has been carried out using conc. H_2SO_4 and conc. HNO_3 to give 4-NH_2(2-NO_2)C_6H_3OMe **(1)**. The treatment of the corresponding anisole with the appropriate acid anhydride or chloride gives acetamide derivatives **(2)**. The acetamide derivative is then treated with PCl_5 in benzene followed by HN_3 in benzene gives 1, 5-disubstituted tetrazole **(3)**. The benzene was evaporated and residue was refluxed in conc. HCl

giving corresponding tetrazole 92%. The catalytic reductions of nitro group containing tetrazoles were carried using PtO_2 in AcOH gives 79% 5-NH_2 analogue **(4)** (Scheme 3.1).



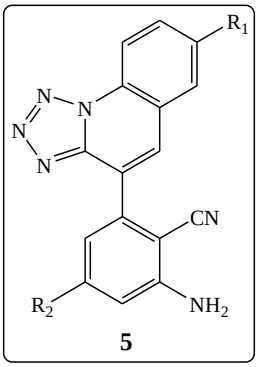
Scheme 3.1: Synthesis of 1, 5-disubstituted tetrazoles

The thermolysis of 1, 5-disubstituted tetrazoles containing Me, NO_2, NH_2 groups on phenyl ring at 200-800 °C leads via isomerization to azides and elimination of N_2 to give singlet nitrenes with subsequent rearrangement to benzimidazoles and carbodiimides.[7] Electronic effects of para substituents in the phenyl ring influenced the thermolysis mechanism. Furthermore, *Klyuev N. A. et al*[8] have reported the thermal decomposition of tetrazoles at 50-600° followed 2 paths: (i) loss of N_2 and formation of MeN=C=NC_6H_4X-*p* (which polymerized to di-, tri- and tetramers) and secondary processes, which formed MeN=C=NMe and *p*-RC_6H_4N=C=NC_6H_4R-*p* and (ii) loss of N_2 and formation of heterocycles, e.g., 2-substituted benzimidazoles and 3-substituted imidazoles.

In 1977, *Klyuev N. A. et al*[9] have reported a Hammett correlation of mass spectral peak intensity ratios of alkyl substituted phenyl tetrazoles (R=H, Me, MeO, EtO, NH_2, Me_2N, Cl, NO_2, CO_2H) indicated that the electronic effects of R were transmitted through the benzene ring during the $M^{+\cdot}$-N_2 fragmentation. Furthermore, *Klyuev N. A. et al*[10] have reported the mass spectral fragmentation of 1-aryl-5-methyltetrazoles.

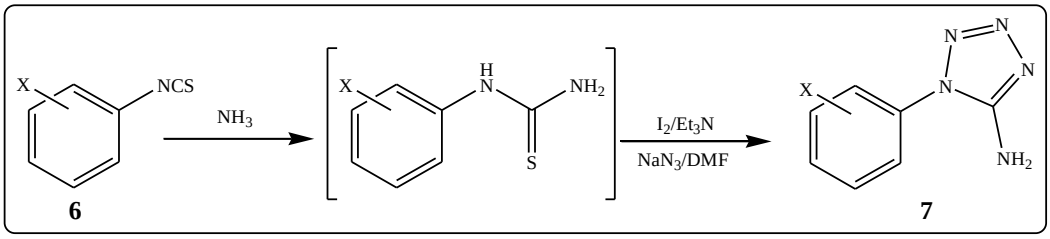
Gross E. G. et al[11] have reported the action of 1-aryl-5-methyltetrazoles and its derivatives causes the depressant action. With iodine in position 5, alkyl groups in position 1 have only anesthetic action, but with longer chains, convulsant activity begins to appear. When the positions of the groups are reversed and alkyls are in 5, only groups above butyl show convulsive activity. Furthermore, they have reported the absorption spectra of various nitro and amino substituted 1, 5-disubstituted tetrazoles and these compounds have been evaluated for their anti-depressant activity.

Patel R. G. et al[12] have synthesized new series of 2-amino-3-cyano-4-tetrazolo-quinolinylpyridine derivatives **(5)** by the one-pot cyclocondensation reaction of a tetrazolo[1, 5-*a*]quinoline-4-carbaldehyde, malononitrile, a heterocyclic/ aromatic methyl ketone and ammonium acetate. These compounds were subjected to *invitro* antimicrobial screening against a panel of pathogenic strains of bacteria and fungi. Some of the compounds were found to be equipotent or more potent than commercial antibiotics as evident from the results.



5

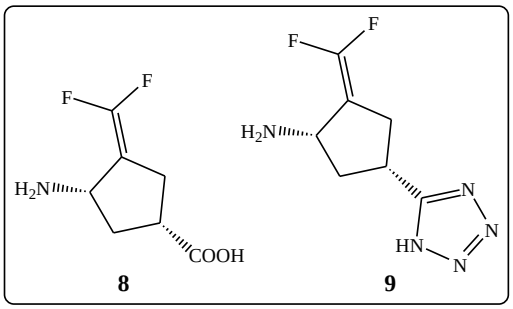
Yella R.et al[13] have successfully prepared a series of 1-aryl-1*H*-tetrazole-5-amine **(7)** from their corresponding isothiocyanates **(6)**. Aryl isothiocyanates containing week deactivating groups in their *ortho*, *meta* or *para* positions reacted efficiently in good yields **(Scheme 3.2)**. Strongly deactivating group (-NO_2) when present in the *m*-position yielded the corresponding tetrazole in good yield.



6 **7**

Scheme 3.2: Synthesis of 5-amino-1-phenyl tetrazoles from isothiocyanates

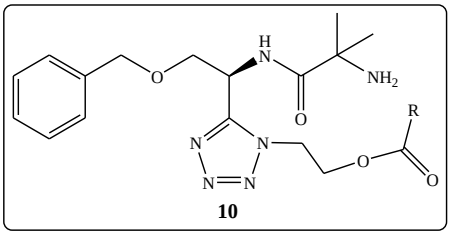
γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system. Low GABA levels are related to a series of neurological disorders including Parkinson's disease. *Yuan H. et al*[14] have reported the synthesis of two analogues of (1S, 3S)-3-amino-4-difluoromethylene- cyclopentane carboxylic acid **(8**) as a potent in activator of GABA-AT. Tetrazole analogue **(9**) has shown to be a time and concentration dependent inhibitor of GABA-AT. It is less potent than the parent compound, although its in vitro potency is higher than that for the antiepilepsy drug vigabatrin. The increased lipophilicity of tetrazole analogue relative to parent compound and to vigabatrin makes it desirable.



8 **9**

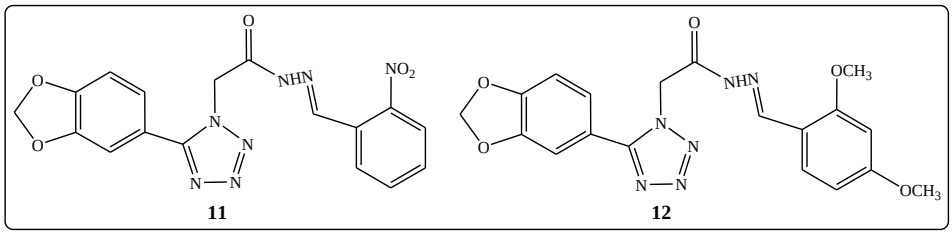
Li J. et al[15] have reported the synthesis of tetrazole-based peptidomimetic 4- (hydroxy-butyl)carbamic acid 2-{5-[1-(2-amino-2-methyl propionylamino)-2- benzyloxyethyl] tetrazol-1-

yl}ethyl ester (BMS-317180) **(10)** as a human growth hormone secretagogue (GHS). A series 1, 5-disubstituted tetrazole containing amine analogues were also described in literature.[16, 17]



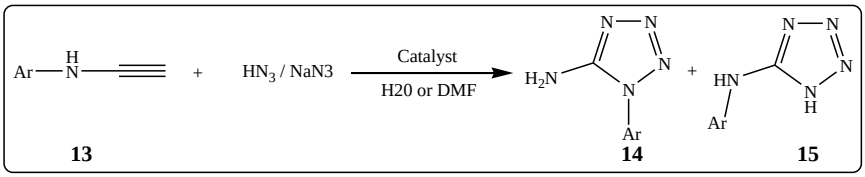
10

Arshad M. et al[18] have reported the synthesis of a series of tetrazolohydrazones starting from piperonyl aldehyde. All the compounds were screened against the ER+/- breast cancer cell lines. Based on the gene study, 1, 5-disubstituted tetrazole containing hydrazone **(11)** and two other were found more effective in retarding the growth of MCF-7 cells. While compound **(12)** showed more growth retarding effects in ER negative MDA-MB-231 and ZR-75 cell lines.



11 **12**

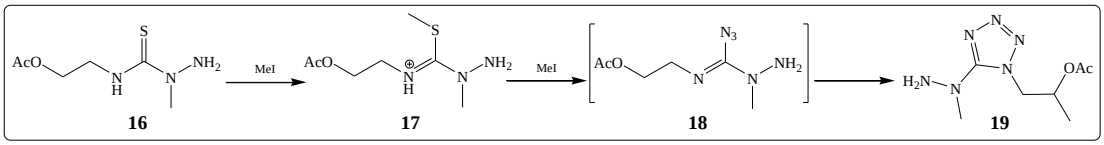
Nasrollahzadeh et al have reported the useful catalytic protocols such as $ZnCl_2$ under aqueous refluxing conditions, [19] $FeCl_3$–SiO_2, [20] and natrolite zeolite, [21] for the preparation of 1-aryl-5-amino-1*H*-tetrazole **(14)** derivatives from arylcyanamides **(13)** and hydrazoic acid or NaN_3 (Scheme **3.3**). Upon exploration of the reaction scope, it was revealed that an electron-releasing substituent on the arylcyanamide was essential for the attainment of stereoselectivities. On the other hand, an arylcyanamide with an electron releasing substituent led to 1-aryl-5-amino-1*H*-tetrazole; however, the reaction was in some cases hampered by the formation of 5-arylamino-1*H*-tetrazole **(15)** as other regioisomeric products.



13 **14** **15**

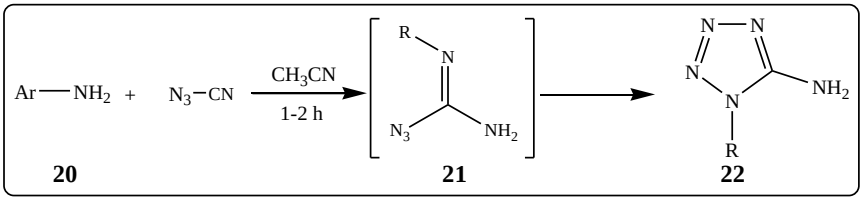
Scheme 3.3: Synthesis of 5-amino-1-aryltetrazoles

The methylated sulfur atom of a thioamide acts as a leaving group in the nucleophilic displacement. *Atherton et al*[22] have used this tactic to introduce an azide group so that the resulting azido amine can produce the corresponding tetrazole via electrocyclic ring closure. This method was recently used by *Banert K et al*[23] for the synthesis of tetrazole **(19)** from them ethylated sulfur atom of 4-[2-(acetoxy)ethyl]-2- methylthiosemicarbazide **(16)** with NaN_3 **(Scheme 3.4)**.



Scheme 3.4: Synthesis of 5-amino-1-alkyltetrazoles via thiosemicarbazide formation

Recently, several commercially available amine **(20)** and hydrazine compounds were reacted with three equivalent of cyanogen azide dissolved in acetonitrile/water solution (4:1) to afford an array of imidoyl azide intermediates **(21)**. Subsequent cyclization led to 1-substituted 5-aminotetrazoles **(22)**. This procedure also wasemployed in the productions of *bis*- and *tris*(1-substituted 5-aminotetrazole) derivatives **(Scheme 3.5)**. These aminotetrazoles were nitrated with 100 % nitric acid to produce mono-, di-, and trisubstituted nitroiminotetrazole derivatives.[24]



Scheme 3.5: Synthesis of 5-amino-1-phenyltetrazoles using cyanogens azide

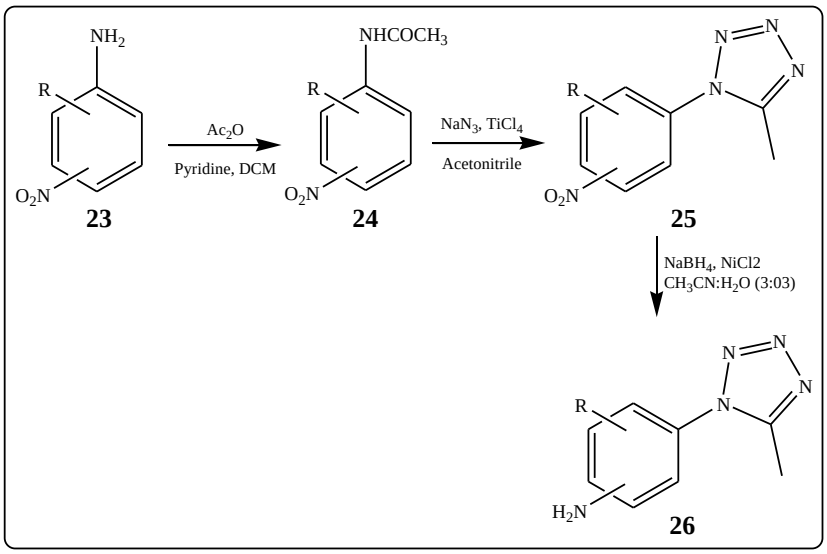
3.2 Present Work

The present study describes an efficient route for the synthesis of a number of 5-methyl-1*H*-tetrazol-1-yl substituted aniline derivatives from the corresponding nitroanilines via. three step reaction.

Step-I: Acylation of nitroaniline to secondary amide using acetic anhydride in dichloromethane.

Step-II: The conversion of secondary amide into 1, 5-disubstituted tetrazole.

Step-III: Reduction of nitro group into amino group using $NaBH_4/NiCl_2$ in water.



Scheme 3.6: Synthesis of substituted (5-methyl-1*H*-tetrazol-1-yl)benzamines

3.3 Result and Discussion

Herein, the synthesis of 5-methyl-1-(nitrophenyl)-1*H*-tetrazole and their analogues were prepared from simple and commercially available nitroanilines and substituted nitroanilines. Step-I, the synthesis of amide bond linkage has been carried out by various methods reported in literature, [25, 26] but *N*-acylation of aromatic amines using acetic anhydride in dichloromethane usingcatalytic amount of pyridine is found to be the most efficient and convenient method for the synthesis of *N*-acyl derivatives in excellent yields at room temperature. Initially, we have carried out acylation of *p*-nitroaniline (1.0 mmol) by stirring with acetic anhydride (1.2 mmol) in the presence of pyridine (0.5 ml)in dichloromethane (20 ml) at room temperature for 4 hrs. giving 98% yield (Table 3.1, entry 1). The reactivity of various nitroanilines with acetic anhydride under the same reaction conditions were examined. The results are summarized in Table **3.1**.

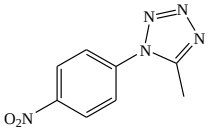
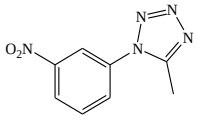
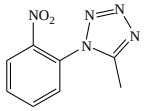
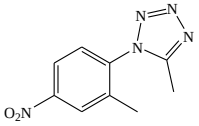
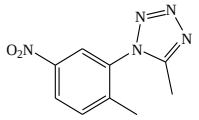
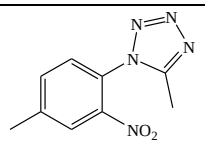
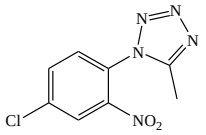
Table 3.1: Acylation of substituted nitroanilines

Entry	Aniline	Product	Time (hr)	Yield (%)	mp (ºC)
25a	4-Nitroaniline	4-Nitroacetanilide	4	98	213-215
25b	3-Nitroaniline	3-Nitroacetanilide	5	96	156-158
25c	2-Nitroaniline	2-Nitroacetanilide	8	92	94-96
25d	2-Methyl-4-Nitroaniline	2-Methyl-4-Nitroacetanilide	6	94	204-206
25e	2-Methyl-5-Nitroaniline	2-Methyl-5-Nitroacetanilide	6	93	90-92
25f	2-Methyl-4-Nitroaniline	2-Methyl-4-Nitroacetanilide	7	93	116-118
25g	2-Chloro-4-Nitroaniline	2-Chloro-4-Nitroacetanilide	10	89	135-137

The reaction of aromatic amines (**23a-g)** using acetic anhydride in the presence of pyridine gives the corresponding acetamides (**24a-g)** in good yields (Table 3.1, entries 1- 7). Aromatic amines with electron-withdrawing groups present at *para*- position gave high yields in less time.

Step-II, the synthesis of 1, 5-disubstituted tetrazoles (**25a-g)** from the corresponding secondary amides (**24a-g)** was carried out by using the reaction described in Chapter-II, where secondary amides react with NaN_3 in acetonitrile in presence of $TiCl_4$ as catalyst.

Table 3.2: Synthesis of 1, 5-disubstituted tetrazoles

Entry	R/NO_2	Product	Time (hr)	Yield (%)	mp (°C)
25a	H, 4-NO_2		6	93	216-218
25b	H, 3-NO_2		7	89	152-154
25c	H, 2-NO_2		9	83	118-120
25d	2-CH_3, 4-NO_2		7	89	177-179
25e	2-CH_3, 5-NO_2		9	83	156-158
25f	4-CH_3, 2-NO_2		6	92	109-111
25g	4-Cl, 2-NO_2		7	91	146-148

Step-III, 5-methyl-1-(4-nitrophenyl)-1*H*-tetrazole and related nitro compounds were reduced by using method reported in literature, [27] where nitro compounds are reduced to amines by $NaBH_4$ as a hydrogenating agent in the presence of $Ni(OAc)_2.4H_2O$ as catalyst in a mixture of CH_3CN:H_2O (3.0:0.3 mL). We applied the optimal conditions for the reduction of a variety of nitro compounds to their corresponding amines, as shown in Table **3.3**.

The product amines were obtained in high to excellent yields within 20–60 minutes. The chemoselective reduction of nitro group was carried without affecting the nitrogen rich tetrazole ring. In all reductions, by the combination of $NaBH_4$ with $Ni(OAc)_2.4H_2O$ in wet CH_3CN, the immediate deposition of a fine black precipitate and the subsequent evolution of hydrogen gas were observed.

Table 3.4 illustrates the IR data of $–NH_2$ stretching frequencies of 1, 5- disubstituted tetrazole containing anilines **(26a-g)** synthesized in the present work. From the table, all the newly synthesized tetrazole containing anilines gave two absorptionband in the range 3150-3400

cm^{-1} for the $–NH_2$ functional group. The IR spectral values obtained for primary amine group ($–NH_2$) present in the compounds **(26a-g)** are in agreement with the values reported in literature.

Table 3.3: Synthesis of substituted (5-methyl-1H-tetrazol-1-yl)benzenamines

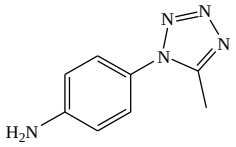
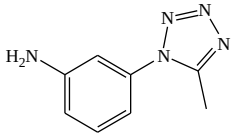
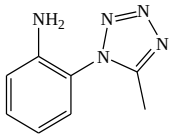
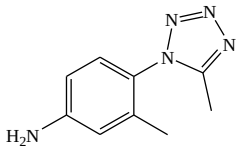
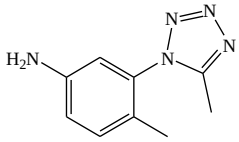
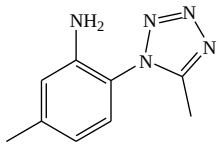
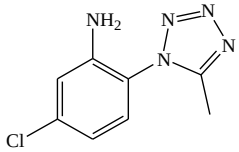
Entry	R/NO_2	Product	Time (min)	Yield (%)	mp (°C)
26a	H, 4-NO_2		20	93	146-148
26b	H, 3-NO_2		20	89	116-118
26c	H, 2-NO_2		25	83	97-99
26d	2-CH_3, 4-NO_2		45	83	176-178
26e	2-CH_3, 5-NO_2		35	91	153-155
26f	4-CH_3, 2-NO_2		50	89	124-126
26g	4-Cl, 2-NO_2		60	82	114-116

Table 3.4 illustrates the IR data of C=N stretching frequencies of 1, 5- disubstituted tetrazole containing anilines **(26a-g)** synthesized in the present work. From the table, it is evident that all the newly synthesized tetrazole compounds gave an absorption band in the range 1590-1630 cm^{-1} for the C=N group of tetrazole ring. The IR spectral values obtained for 1, 5-disubstituted tetrazoles in the present work are in agreement with the values reported in literature.[28]The absorption bands for the N=N functional group of the newly synthesized 1, 5-disubstituted tetrazoles (**26a-g**) are presented in the table.

Table 3.4: Characteristic IR absorptions of substituted (5-methyl-^{1}H-tetrazol-1-yl)benzenamines

Compounds	Characteristic Absorption Frequencies (cm^{-1})				
	$-NH_2$	**C=N**	**N=N**	**N-N=N**	**Tetrazole ring**
26a	3384, 3190	1601	1485	1238	1097, 1118
26b	3367, 3153	1609	1472	1226	1091, 1110
26c	3371, 3159	1620	1493	1223	1099, 1129
26d	3379, 3161	1629	1481	1212	1079, 1108
26e	3372, 3165	1619	1470	1217	1072, 1131
26f	3398, 3173	1606	1497	1215	1081, 1113
26g	3412, 3186	1633	1489	1256	1088, 1105

Table 3.4 inferred that all the newly synthesized compounds showed an absorption band between 1450-1500 cm^{-1}, which confirms the presence of N=N functional group. These values are in agreement with the values reported in literature.[29] Furthermore, the appearance of an absorption band around 1250-1300 cm^{-1} reveals that there is N-N=N linkage present in a molecule. In the present work, similar observations are found with regard to the presence N-N=N linkage of tetrazole ring. The IR absorptions at 1238 cm^{-1}, 1226 cm^{-1}, 1223 cm^{-1}, 1212 cm^{-1}, 1217 cm^{-1}, 1215 cm^{-1}, and 1256 cm^{-1} are due to the presence of N-N=N functional groups present in the compounds (**26a-g)** respectively. The table **3.4** also presents the data of tetrazole ring frequencies of the newly synthesized compounds (**26a-g**).

These values are also in accordance with the values of tetrazole ring reported in litetrature.[30] The presence of C-Cl linkage in the compound **(26g)** is confirmed due to the presence of absorption bands at 768 cm^{-1}.

Furthermore, the evidence for the formation of the substituted (5-methyl-1H- tetrazol-1-yl)benzenamines **(26a-g)** were obtained from the ^{1}H-NMR and ^{13}C-NMR spectra which proved to be the diagnostic tool for the positional elucidation of the proton and carbon atoms respectively.[31] The Table **3.5** given below presents the data of chemical shifts of proton in the ^{1}H-NMR spectra of the substituted (5-methyl-1H- tetrazol-1-yl)benzenamines (**26a-g**).

A significant fact of the data given in **Table 3.5** indicates a signal of two protons in the range of δ 3.93 – 4.56 for primary aromatic amine. Aromatic protons were found in the range of δ 6.91 – 7.63. The aromatic protons *ortho* to the tetrazole ring in compound **26a** are found at δ 7.46 whereas the protons *ortho* to the primary amine group were found at δ 6.94. This indicates that the benzene protons *ortho* to the tetrazole ring are deshielded by δ 0.52 ppm relative to the

protons *ortho* to amine group. The deshielding effect may be attributed to the presence of methyl group in the first position of tetrazole ring. In the compound **(26d-g),** all the three protons of aromatic ring gave three different signals. The presence of electron donating group at second position of the tetrazole ring, incompounds **26d**, **26e** and **26f**, considerably diminishes or disappears the deshielding effect. Similar type of observations was reported previously for the tetrazole containing aromatic compounds.[32]

Table 3.5 Chemical shifts of ^{1}H-NMR spectra of the substituted (5-methyl-1H- tetrazol-1-yl)benzenamines

Compound	Chemical Shift (δ ppm)			
	–NH_2 (s)	**-H (Ar)**	**-CH_3 (Ar)(s)**	**5-CH_3 (Tetrazole)(s)**
26a	4.38	7.20 (d, 2H), 6.80 (d, 2H),	---	2.56
26b	4.08	7.30-7.32 (m, 1H), 6.84-6.86 (m, 1H), 6.75-6.77 (m, 2H).	---	2.62
26c	3.93	7.36-7.38 (m, 1H), 7.09-7.11 (m, 1H), 6.91-6.91 (m, 2H).	---	2.53
26d	4.04	6.95-6.97 (m, 1H), 6.62-6.64 (m, 2H).	2.42	1.93
26e	4.11	7.30-7.32 (m, 1H), 7.21-7.23 (m, 1H), 6.99-7.01 (m, 1H).	2.39	1.94
26f	4.33	7.27-7.29 (m, 1H), 7.23-7.25 (m, 1H), 6.91-6.93 (m, 1H).	2.40	1.97
26g	4.56	8.03-8.05 (m, 1H), 7.63-7.65 (m, 1H), 7.21-7.73 (m, 1H).	---	2.51

The ^{1}H NMR spectrum of the compound, viz., 3-(5-methyl-1*H*-tetrazol-1-yl)-benzenamine **(26b)** shows expected signals. A multiplet observed in the region δ 7.31 may be assigned to the proton of the aromatic ring present on carbon atom *ortho* to both tetrazole ring and amine group.Apart from this, two signals are observed in aromatic region, one is at δ 6.85 as multiplet for the proton *ortho* tetrazole ring and another one multiplet appears at δ 6.76 for two aromatic protons *para* and *meta* positions to tetrazole ring. The ^{1}H NMR spectrum also shows

two different singlets, one appears at δ 2.62 for methyl group protons and second for primary aromatic amine group at δ 4.08.

The similar types of observations are found for the other synthesized compounds. Hence, the ^{1}H-NMR spectra of the synthesized compounds lend convincing evidence to the assigned structure. Further confirmation was done with ^{13}C NMR spectra.

The ^{13}C NMR spectrum of the compound, viz., 3-(5-Methyl-1*H*-tetrazol-1-yl)-benzenamine **(26b)** shows expected signals. In this compound, the tetrazole carbon resonates at 151.40 ppm. A carbon signal appeared at 9.85 ppm may be due to the presence of CH_3 group on the tetrazole ring. The carbon atom aromatic ring having NH_2 group shows a signal at 148.07 ppm. The other carbon atoms of aromatic ring are observed around 113.73 – 134.56 ppm. The similar types of observations are found in case of other tetrazole containing anilines. Finally the structures of the compounds **26a-g** are confirmed from the molecular ion peak with the corresponding molecular weight of the compounds.

3.4 Experimental

All the chemicals were purchased from commercial suppliers where as secondary amides, 1, 5-disubstituted tetrazoles and tetrazole containing amines were synthesized in our laboratory. The melting points cited in this chapter were determined in open capillaries using melting point apparatus (Model MP-96) and reported in degree centigrade. The progress of reaction and purity of the product were monitored by thin layer chromatography using precoated Silica 60/UV_{254}(SDFCL). ^{1}H NMR was recorded using 400 MHz Varian Mercury plus 400 MHz FT NMR spectrometer in $CDCl_3$. The ^{1}H chemical shift values were reported on the δ scale in ppm, relative to TMS (δ = 0.00 ppm). IR spectra were recorded and reported in cm^{-1}.

3.5.1 General procedure for the synthesis of secondary amides (24a-g)

4-Nitroaniline 23a (1 mmol) was taken into a 50 ml round bottomed flask containing 10 ml dichloromethane and to it acetic anhydride (1.2 mmol) was added drop wise with stirring. The reaction mixture was stirred for time given in Table 3.1. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure and precooled water was added to it. Then crude product was neutralized by dil. HCl with stirring for 30 min. The solid product was filtered off and purified by recrystalization using aqueous ethanol (60%) to obtain pure 4-Nitroacetanilide 24a in the form of pale yellow crystalline solid (1.2 g, 98%, mp 58-60°C (Lit. mp 114-115°C).

All the other synthesized compounds were characterized by comparing with their melting point reported in literature (Table. **3.1**).

3.5.2 General procedure for the synthesis of 1, 5-disubstituted tetrazole (25a-g)

To a stirred solution of 4-nitroacetanilide **24a** (2gm, 0.5moles) in dry acetonitrile (5ml) at 0-5ºC, $TiCl_4$ (2.8gm, 1.0 moles) was added dropwise with stirring and the mixture was stirred at

room temperature for 30 min. Then sodium azide (0.93gm, 0.5 mol.) was added to it and the reaction mixture was heated at 80-90ºC. After 2 hr remaining amount of sodium azide (0.93gm, 0.5 mol.) was added to reaction mixture and heating was continued for 4-6 hrs. The reaction was monitored by TLC after 3hrs. Then the reaction mixture was cooled and poured over crushed ice and the product **25a** separated out was filtered, washed with water, dried and recrystallized from aq. ethanol.

Similarly other 1, 5-disubstituted tetrazoles were synthesized. The reaction time and physical constants are recorded in Table **3.2**.

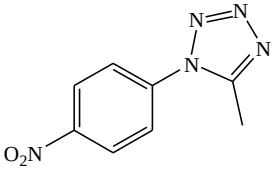
3.5.3 General procedure for the synthesis of (5-methyl-1*H*-tetrazol-1-yl)benzenamines (26a-g)

To a solution of 5-methyl-1-(4-nitrophenyl)-1*H*-tetrazole **25a** (0.5 g, 1 mmol) in CH_3CN-H_2O (3:0.3 ml) in a round-bottomed flask (25 ml), $NiCl_2.6H_2O$ (0.12 g, 0.2 mmol) was added and the mixture was stirred for 5 min. Then, a fine powder of $NaBH_4$ (0.37g, 4 mmol) was added to the reaction mixture in portion with stirring results formation of the black precipitate in reaction mixture. After complete addition of $NaBH_4$, the mixture was stirred for 30 min and the progress of the reaction was monitored by TLC. At the end of reaction, distilled water (5 ml) was added to the reaction mixture and the mixture stirred for 10 min. The mixture was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give crude solid product **26a**. The crude product was purified by recrystalization usingaq. ethanol.

Similarly other (5-methyl-1*H*-tetrazol-1-yl)benzenamines were synthesized. The reaction time and physical constants are recorded in Table **3.3**.

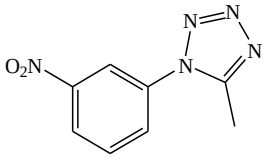
5-Methyl-1-(4-nitrophenyl)-1H-tetrazole (25a)

mp. 216 ºC. ^{1}H-NMR ($CDCl_3$): δ 8.24 (d, 2H), 8.17 (d, 2H), 3.89 (s, 3H). FT-IR (KBr, cm^1): 3097, 3078, 2941, 2870, 1610, 1587, 1527, 1485, 1410, 1346, 1288, 1116, 1095, 995, 871, 813, 746.



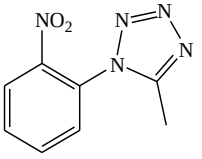
5-Methyl-1-(3-nitrophenyl)-1H-tetrazole (25b)

mp. 216 ºC. ^{1}HNMR ($CDCl_3$): δ 8.40-8.46 (m, 2H), 8.10-8.13 (m, 1H), 7.80-7.82 (m, 1H), 2.49 (s, 3H). IR (KBr, cm^1): 3080, 2997, 1614, 1583, 1527, 1496, 1435, 1354, 1298, 1109, 1080, 1030, 910, 842, 806, 752.



5-Methyl-1-(2-nitrophenyl)-1H-tetrazole (25c)

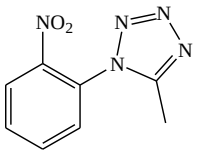
^{1}H-NMR ($CDCl_3$): δ 8.40-8.42 (m, 1H), 8.20-8.23 (m, 1H), 7.92-7.94 (m, 1H), 7.74-7.76 (m, 1H), 2.15 (s, 3H). IR (KBr, cm^{-1}): 3093, 2989, 1608, 1581, 1527, 1496,



1411, 1344, 1305, 1280, 1257, 1112, 1089, 1024, 987, 854, 750, 723

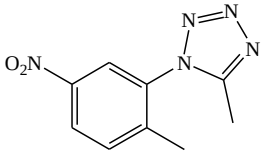
5-Methyl-1-(2-methyl-4-nitrophenyl)-1H-tetrazole (25d)

^{1}H-NMR ($CDCl_3$): δ8.30 (d, 1H) 7, 8.25 (s, 1H); 7.50 (d, 1H); 2.48 (s, 3H), 2.20 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 9.06, 17.74, 122.5, 126.72, 128.1, 137.58, 137.76, 149, 152.44. IR (KBr, cm^1): 3078, 3021, 2980, 2947, 1613, 1585, 1524, 1501, 1422, 1354, 1302, 1289, 1263, 1119, 1079, 1016, 981, 850, 756, 720.



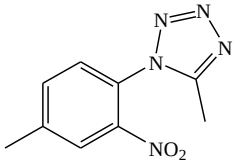
5-Methyl-1-(2-methyl-5-nitrophenyl)-1H-tetrazole(25e)

^{1}H-NMR ($CDCl_3$): δ 8.34 (s, 1H), 8.15 (d, 1H); 7.62 (d, 1H), 2.25 (s, 3H), 2.15 (s, 3H). IR (KBr, cm^1): 3073, 3027, 2998, 2961, 1622, 1583, 1514, 1492, 1409, 1361, 1299, 1277, 1253, 1108, 1069, 1008, 985, 851, 752, 727



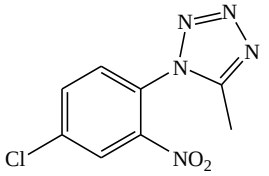
5-Methyl-1-(5-methyl-2-nitrophenyl)-1H-tetrazole(25f)

^{1}HNMR ($CDCl_3$): δ 8.46 (d, 1H), 8.27 (s, 1H), 7.78 (d, 1H), 2.25 (s, 3H), 2.14 (s, 3H). IR (KBr, cm^1): 3089, 3048, 2972, 2957, 1617, 1589, 1517, 1492, 1406, 1338, 1299, 1273, 1245, 1117, 1078, 1019, 976, 861, 756, 731



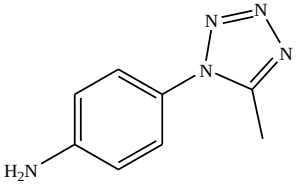
1-(4-Chloro-2-nitrophenyl)-5-methyl-1H-tetrazole(25g)

^{1}HNMR ($CDCl_3$): δ 8.27 (d, 1H), 7.89 (s, 1H); 7.55 (d, 1H), 2.51 (s, 3H). ^{13}CNMR ($CDCl_3$): δ 9.0, 125.4, 126.6, 130.6, 134.9, 138.8, 145.0, 153.3. IR (KBr, cm^1): 3080, 3060, 2976, 2946, 1621, 1578, 1510, 1493, 1403, 1341, 1301, 1270, 1241, 1107, 1084, 1016, 986, 857, 753, 721



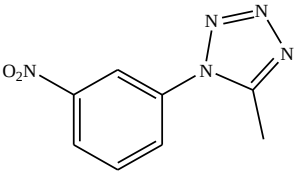
4-(5-Methyl-1H-tetrazol-1-yl)benzenamine (26a)

^{1}H NMR ($CDCl_3$): δ 7.20 (d, 2H), 6.80 (d, 2H), 4.38 (s, 2H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 9.6, 115.1, 124.0, 126.0; 148.4, 151.7. IR (KBr, cm^{-1}): 3384, 3190, 3041, 2983, 1601, 1573, 1527, 1485, 1340, 1238, 1118, 1097, 847, 819, 748



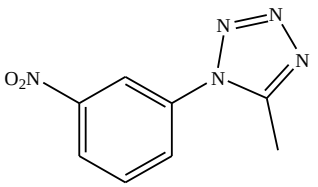
3-(5-Methyl-1H-tetrazol-1-yl)benzenamine (26b)

^{1}HNMR ($CDCl_3$): δ 7.30-7.32 (m, 1H), 6.84-6.86 (m, 1H), 6.75-6.77 (m, 2H), 4.08 (s, 2H); 2.62 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 10.0, 110.6, 113.7, 116.5, 130.5, 134.5, 148.1, 151.4. IR (KBr, cm^{-1}): 3367, 3153, 3056,



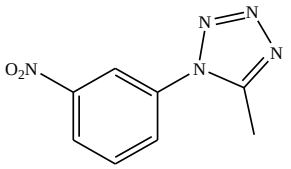
2967, 1609, 1588, 1531, 1472, 1334, 1226, 1110, 1091, 864, 827, 755.

2-(5-Methyl-1H-tetrazol-1-yl)benzenamine (26c)



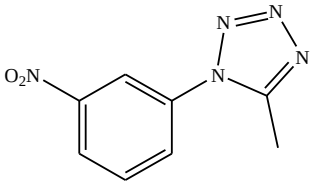
^{1}H-NMR ($CDCl_3$): δ 7.36-7.38 (m, 1H), 7.09-7.11 (m, 1H), 6.91-6.91 (m, 2H), 3.93 (s, 2H), 2.53 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 9.2, 117.4, 118.8, 119.1, 126.8, 131.8, 142.1, 153.0. IR (KBr, cm^{-1}): 3371, 3159, 3050, 2958, 1620, 1598, 1529, 1493, 1327, 1223, 1129, 1099, 848, 816, 745.

3-Methyl-4-(5-methyl-1H-tetrazol-1-yl)benzenamine (26d)



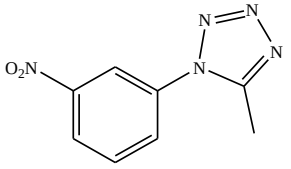
^{1}H-NMR ($CDCl_3$): δ 6.95-6.97 (m, 1H), 6.62-6.64 (m, 2H), 4.04 (s, 2H); 2.42 (s, 3H); 1.93 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 9.0, 17.3, 112.8, 116.6, 122.7, 127.7, 136.2, 148.8, 152.9. IR (KBr, cm^{-1}): 3379, 3161, 3054, 2982, 1629, 1601, 1511, 1481, 1317, 1212, 1108, 1079, 854, 821, 751.

4-Methyl-3-(5-methyl-1*H*-tetrazol-1-yl)benzenamine (26e)



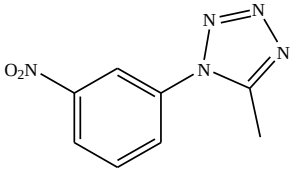
^{1}H-NMR ($CDCl_3$): δ 7.30-7.32 (m, 1H), 7.21-7.23 (m, 1H), 6.99- 7.01 (m, 1H), 4.11 (s, 2H), 2.39 (s, 3H), 1.94 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 8.9, 16.1, 112.7, 117.7, 123.8, 132.2, 132.9, 145.8, 152.5. IR (KBr, cm^{-1}): 3372, 3165, 3051, 2974, 1619, 1600, 1517, 1470, 1312, 1217, 1131, 1072, 853, 826, 748.

5-Methyl-2-(5-methyl-1H-tetrazol-1-yl)benzenamine (26f)



^{1}H-NMR ($CDCl_3$): δ 7.27-7.29 (m, 1H), 7.23-7.25 (m, 1H), 6.91-6.93 (m, 1H), 4.33 (s, 2H); 2.40 (s, 3H); 1.97 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 9.1, 21.4, 116.9, 119.7, 122.3, 127.5, 132.8, 142.3; 153.1. IR (KBr, cm^{-1}): 3398, 3173, 3067, 2988, 1634, 1606, 1517, 1497, 1324, 1256, 1113, 1081, 859, 829, 758.

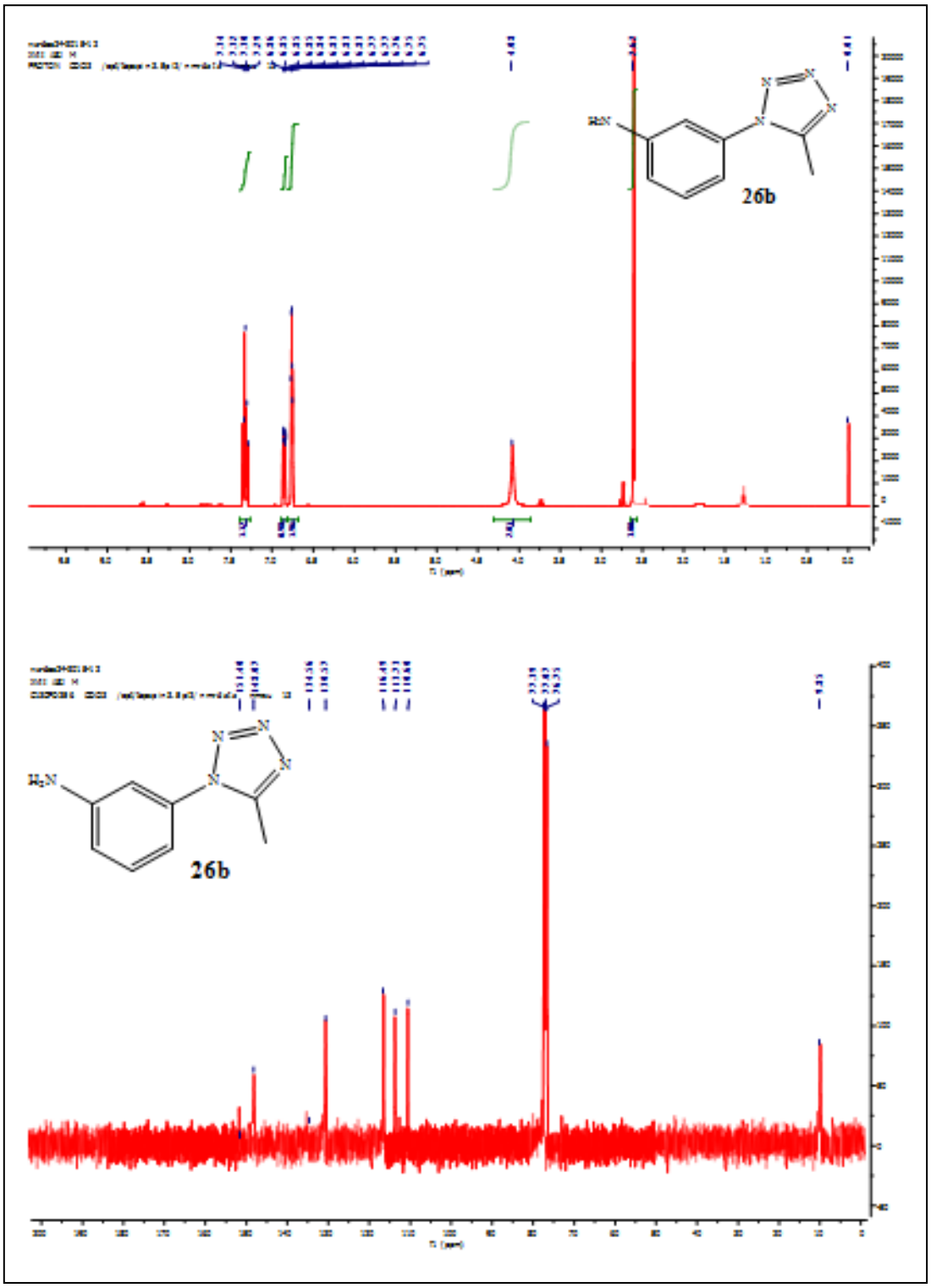
3-Chloro-4-(5-methyl-1H-tetrazol-1-yl)benzenamine (26g).

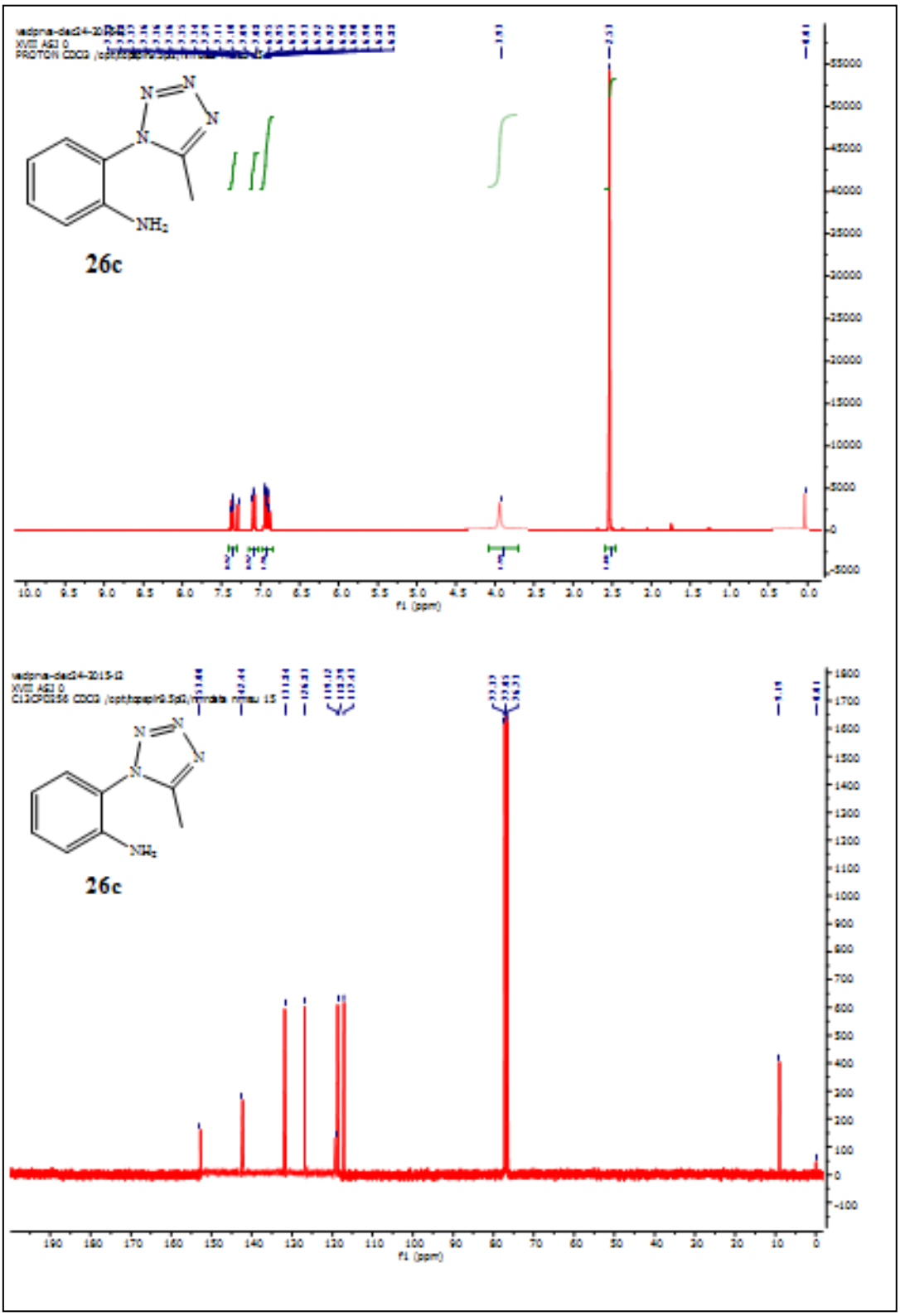


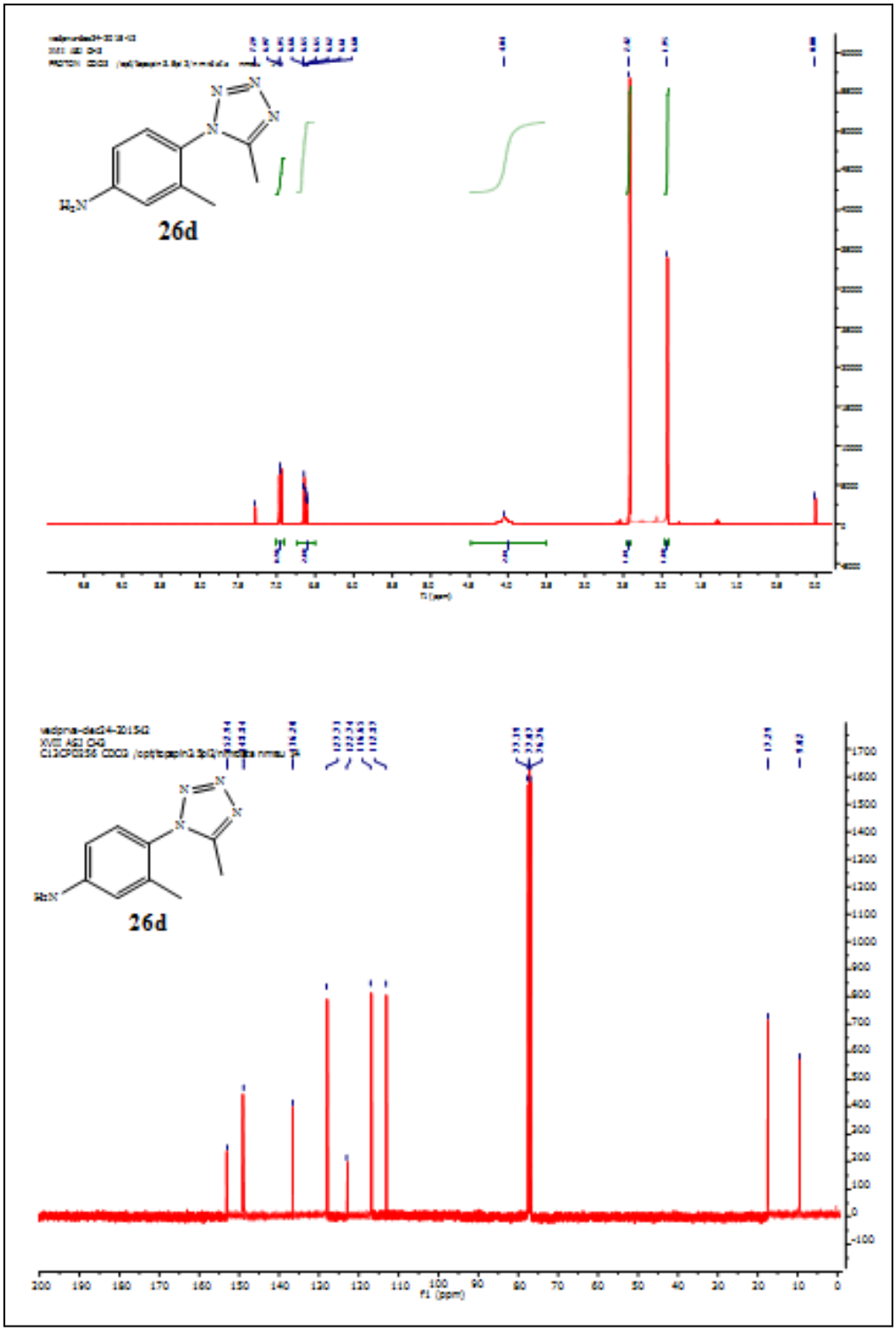
^{1}H-NMR ($CDCl_3$): δ 8.03-8.05 (m, 1H), 7.63-7.65 (m, 1H), 7.21- 7.73 (m, 1H), 4.56 (s, 2H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 9.1, 114.1, 116.3, 122.2, 132.1, 142.2, 149.3, 152.0. IR (KBr, cm^{-1}): 3412, 3186, 3070, 2972, 1633, 1601, 1513, 1489, 1321, 1211, 1105, 1088, 863,

831, 768, 744.

Selected Spectra




26c
f1 (ppm)
26c
f1 (ppm)



3.6. Conclusion

Aromatic amines are essentially important intermediates in synthetic organic and medicinal chemistry. They play a vital role in the synthesis of heterocyclic compounds such as triazole, imidazole, pyrazole etc. and other compounds like Schiff bases, amides etc. The insertion of one or more heterocycles in the aromatic amines enhances the bioactivity of the resultant molecules. 4-(5-Methyl-1*H*-tetrazol-1-yl)benzenamine and related compounds **(26a-g)** may acts as starting material for new bioactive compounds, since several modifications of the

amine groups are possible. Many different methods have been used to achieve the target molecules. Herein, we have described the synthesis of 4-(5-Methyl-1*H*-tetrazol-1-yl)benzenamine and related compounds from commercially available nitroanilines via multi-step reactions.

The acylation of nitroanilines by using acetic anhydride leads to the formation of nitroacetanilides **(24a-g)** which on reaction with NaN_3 in the presence of $TiCl_4$ in acetonitrile gives 1, 5-disubstituted tetrazole containing nitrobenzenes **(25a-g)** in good to excellent yields. The compounds **(25a-g)** on reduction using $NaBH_4$ gives corresponding (5-Methyl-1*H*-tetrazol-1-yl)benzenamines **(26a-g)**. All the 1, 5-disubstituted tetrazole containing anilines absorbs infrared radiation in the range of 3200- 3400 cm^{-1} the region where primary NH_2 absorbs. The synthesized anilines (26a-26g) were confirmed by using IR, ^1H NMR, ^{13}C NMR, melting point and comparing with literature.

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CHAPTER 4
SYNTHESIS OF SUBSTITUTED 1, 2-BIS(4-(5-METHYL-1*H*-TETRAZOL-1-YL)PHENYL)-DIAZENES

Introduction:

In 1858, Griss developed the azo coupling reaction and obtained first azo dye – Aniline Yellow. Now day, around 10 thousands of these compounds are described in literature and more than 2 thousands are applied to color various materials. Azo compounds are characterized by the presence of the azo group (–N=N–) in their structure, conjugated with two, distinct or indistinct, aromatic or heteroaromatic systems. Azobenzene, with two phenyl rings separated by an azo (–N=N–) group, is the parent molecule for a broad class of aromatic azo compounds. These chromophores are versatile molecules, and have received much interest in research areas both fundamental and applied. The strong electronic absorption maxima can be customized by ring substitution to fall anywhere from the ultraviolet (UV) to visible red regions, allowing chemical fine- tuning of colour.

Because of their specific physico-chemical properties and biological activities, aromatic azo compounds have found a broad application in pharmaceutical, cosmetic, food, dyeing or textile industry and analytical chemistry. These compounds are used as acid-base indicators, biological stains, pigments[1] and commercial colourant for plastics, cosmetics, [2] clothing, and food beverages. However, the most typical and popular field of utility remains their colouring function. Azo dyes are the largest and the most versatile class of dyes.

Many azo-dyes, a major class of dye, such as methyl red, methyl orange, and Congo red, can be used as acid-base indicators. This is due to their ability to function as weak acids or bases. The colour changes are caused by changes in extent of delocalization of electrons: more delocalization shifts the absorption maxima to longer wavelengths and makes the light absorbed redder, while less delocalization shifts the absorption maxima to shorter wavelengths. The azo dyes, like Sudan red and scarlet red, can be used as biological dyes because they are fat-soluble and can be absorbed into fat cell tissues on microscope slides. 60-70% of all synthetic dyes used as commercial colorants are Azo dyes.

The appearance of diverse classes of synthetic dyes including azo dyes occurred due to constant effort to find specific dye for application in diverse materials of industrial importance which include, but not limited to textile fabric, [3] ink-jet printer, [4] paper, leather, aluminium sheet.[5] Furthermore, azo compounds also have many applications in photo-industry such as photodynamic therapy, photographic or electro-photographic systems and are dominant organic photoconductives.[6, 7]

Azo compounds, apart from colourant property, are known to exhibit a variety of interesting biological activities such as inhibition of DNA, RNA and protein synthesis, carcinogenesis and nitrogen fixation.[8-10] Evans Blue and Congo Red are being studied as HIV inhibitors of viral replications.[11] This effect is believed to be caused by binding of azo dyes to both protease and reverse transcriptase of this virus.[12] The existence of an azo moiety in different types of compounds has caused them to show antibacterial and pesticidal activity.[13, 14]

Azo compounds are well known for their medicinal importance and are recognized for their applications as antidiabetics, [15] antiseptics, [16] antineoplastics, [17] antibacterial, [18, 19] and antitumor.[6] Some azo compounds bearing imine linkage displays admirable biological activities as reported in literature.[20, 21] Recently, azo group containing compounds are reported for their antimicrobial activity.[22-24]

4.1 Literature Survey

Synthesis of most azo compounds involves diazotization of a primary aromatic amine, followed by coupling with one or more nucleophiles. Because of the variety of applications, azo compounds, it is interesting to study synthesis of aromatic azo compounds and their derivatives in order to explore the newer potentials of such compounds. Few times azo compound is often described as a chromogen in the literature.[25] The amino- and hydroxy- groups are commonly used coupling components.[26]

Despite of diazotization, Azobenzene can be obtained by: (i) reduction of aromatic compounds having a nitro group (ii) oxidation of aromatic primary amines; (iii) coupling of primary aryl amines with nitroso compounds (Mills reaction);[62, 63] (iv) oxidation of hydrazo derivatives;[64] and (vi) reduction of azoxybenzene derivatives.[65, 66] The methods involving reduction of aromatic nitro compounds and oxidation of aromatic primary amines are useful for the synthesis of symmetrical azobenzene derivatives.

The oxidation of primary aromatic amines becomes the most useful method for the synthesis of symmetrical azobenzene derivatives. Different oxidizing agents such as MnO_2, [27] $KMnO_4$, [28] H_3BO_3, [29] and Hg/I_2, [30] etc. are reported to give azo compounds from aromatic amines. Other metal oxides such as Ag_2CO_3, [31] Ag_2O, [32] $AgMnO_4$, [33] Ni- peroxide, [34] $NaBO_3$, [110] $Pb(OAc)_4$, [35] $Ce(OH)_3$ H_2O, [36] BBCP, [37] or KO_2, [38] hypervalent iodides such as $PhI(OAc)_2$, [39a] $RuCl_3/H_2O_2$, [39b] and aerial oxidants such as O_2-t-BuOK, [40] O_2-Cu_2Cl_2-pyridine, [41] O_2-Co_3O_4, [42] or peroxidase-H_2O_2[43] are also used as oxidizing agents.

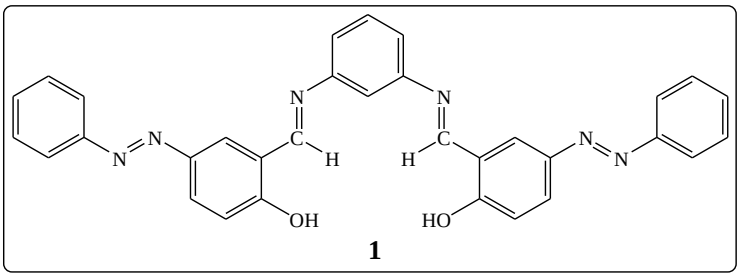
The reductive coupling of nitrobenzenes for the synthesis of symmetrical azobenzene derivatives has been reported with reducing agents, such as zinc in a basic medium, [44] $LiAlH_4$, [45] $NaBH_4$, [46] sodium 2-hydroxy ethoxide in ethylene glycol, [47] catalytic transfer hydrogenation using $Pb/CH_3CO_2NH_4$, [48] Pb/HCO_2NH_4, [49] $SnCl_2$/NaOH, [50] $In(OTf)_3/Et_3SiH$ in DMF, [51] Bi-KOH, [52] glucose in a basic medium[53] etc. Furthermore, The reducing agents like Mg/HCO_2HNEt_3, [54] Al/NaOH under ultrasonic conditions, [55] $TiCl_4/LiAlH_4$, [56] $Co_2(CO)_8$, [57] $NaBH_4/(PhTe)_2$, [58]

$NiCl_2.H_2O$-DTBB, [59] and magnesium diisopropylamide[60] etc. can be used frequently for the synthesis of azobenzene by reduction of nitro compounds. Recently, the reduction of nitrobenzenes has been carried to achieve azobenzene on gold nanoparticles supported on ZrO_2 with visible or ultraviolet light irradiation.[61]

3-N-(4`-Hydroxy-3`-substituted phenyl) carbamoyl-1-methylpyridinium iodide derivatives revealed the most potent analgesic and anti-inflammatory activities in comparison to sulfasalazine and 5-amino salicylic acid. Sulphasalazine, an azo- compound derived from sulphapyridine and 5-aminosalicylic acid has been the only valuable non-corticosteroid drug used in the treatment of inflammatory bowel disease. Azo compounds having sulphasalazine moiety has found to be biologically active used for the treatment of inflammation where metabolite sulphapyridine was largely responsible for the side-effects of sulphasalazine.[2] The transition metal complexes of 2- [2-Hydroxyphenylazo]-1-naphthol-4-sulphonic acid (HPANS) with iron, cobalt and copper show good antibacterial activity against *S. aureus, B. cereus, E. coli, E. cloacae, E. faecalis* and antifungal activity against *C. albicans.*[67]

Eissa H.H.[68] has reported the synthesis of new azo Schiff bases **(1)** prepared by condensation of 3-formyl-4-hydroxy phenyl azobenzene with 1, 3-diamino xylene and 2, 6-diamino Pyridine and evaluated for their antibacterial activities against Gram positive (Bacillus subtilis and Staphylococcus aureus) and Gram negative bacteria (Salmonella typhi and Escherichia coli). The azo compound ligands have exhibited a variable activity of inhibition on the growth of the bacteria.

In the synthetic exploration of 2-amino benzothiazole derivatives, *Keerthi Kumar C.T. et al*[69] have reported the synthesis of several new azo dyes **(4)** by diazotization of 2- amino benzothiazole **(2)** followed by coupling with different coupling compounds such as naphthol derivatives **(3)**, 8-hydroxy quinoline and N, N-dimethyl aniline. The newly synthesized compounds were screened for their antimicrobial activity by well plate method (zone of inhibition). Antioxidant studies of the synthesized compounds were also performed by measuring the DPPH radical scavenging assay and metal chelating method. Results revealed that the compound shows better antibacterial and antioxidant property.



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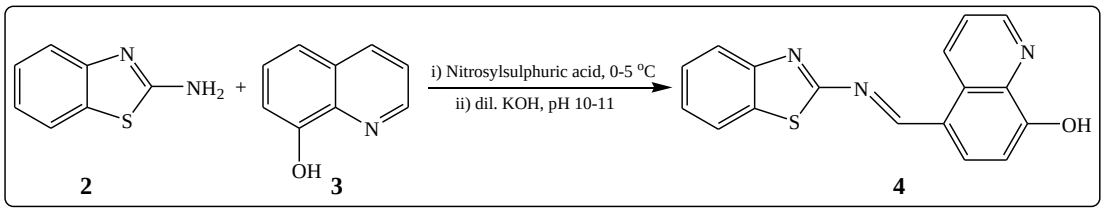
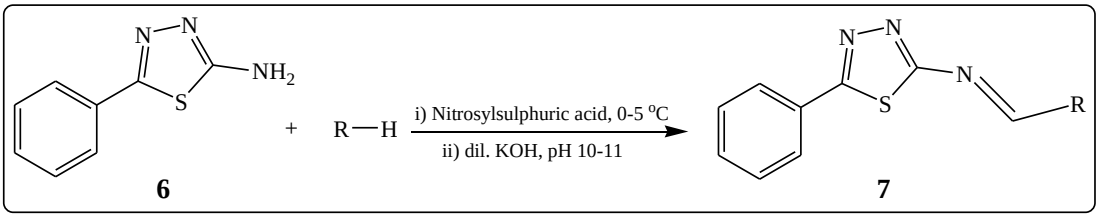


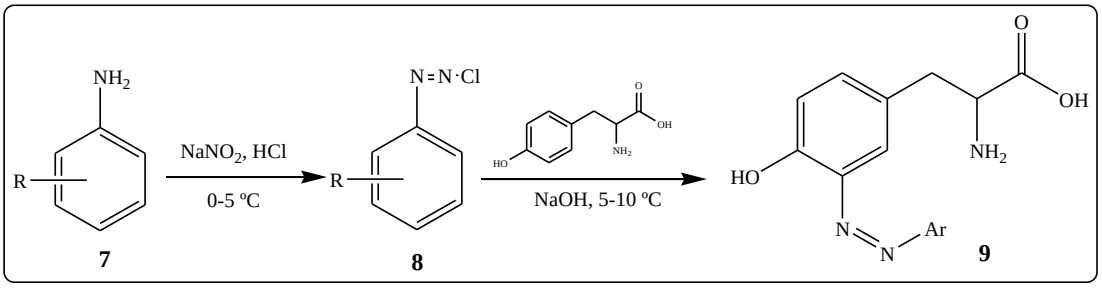
Scheme 4.1: Synthesis of benzothiazole azo dyes

In continuation of their work, *Keerthi Kumar C. T. et al*[70] have reported that the synthesis of a series of heterocyclic azo dyes **(6)** by diazotization of 5-phenyl-1, 3, 4- thiadiazole-2-amine **(5)** by nitrosyl sulphuric acid followed by coupling with different coupling compounds such as 8-hydroxyquinoline, 2, 6-diaminopyridine, 2-naphthol, *N, N*- dimethyl aniline, resorcinol, and 4, 6-dihydroxypyrimidine. These new classes of heterocycles exhibit significant antimicrobial and antioxidant activities. 1, 3, 4-Thiadiazol azo dye coupled with 8-hydroxy quinoline showed higher active antioxidant capacity than 1, 3, 4-thiadiazol azo dye coupled with naphthol.

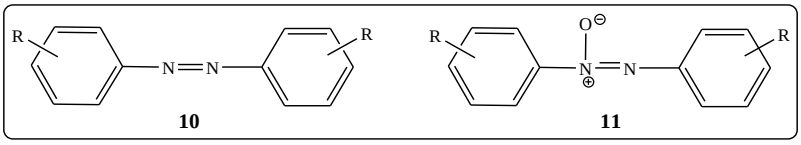


Scheme 4.2: Synthesis of thiadiazole azo dyes

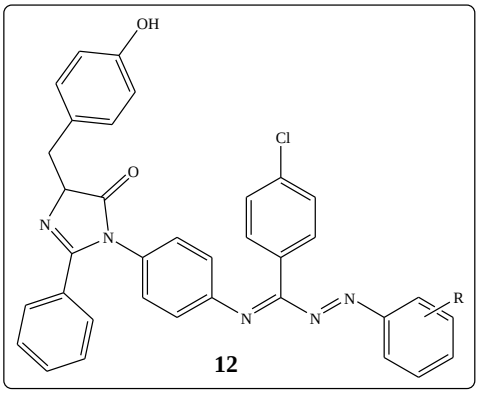
Pagariya R.F. et al[71] have synthesized a series of tyrosine based azo compounds **(9)** in excellent yields via the diazotization of different aromatic amines **(7)** followed by coupling with Tyrosine. The synthesized compounds have been tested in vitro against human pathogens in order to assess their antibacterial properties using disk diffusion method. The compounds analyzed for its antibacterial action showed moderate to extraordinary inhibitory effect at most of the concentrations against all the tested pathogens.



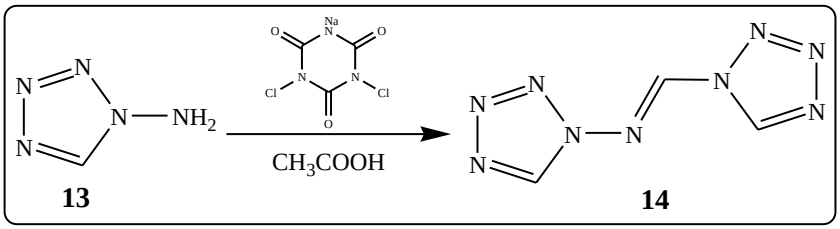
Takahashi H. et al[72] have reported the preparation of a series of substituted phenylazo **(10)** and phenylazoxy **(11)** compounds and their anti-androgenic activity has been measured in terms of i) the growth-inhibiting effect on an androgen-dependent cell line, SC-3, and ii) the binding affinity to nuclear androgen receptor. Commonly, azo/azoxy compounds showed cell toxicity, and the growth-inhibiting effects on SC-3 cells correlated with the toxicity. However, these compounds possessed potent anti- androgenic activity without apparent cell toxicity.



Dodiya D. K. et al[73] have reported the synthesis of a series of novel azo compounds bearing imidazolyl moiety **(12) and** evaluated for their antimicrobial activity. The compounds (3a-h) were evaluated for their antibacterial activity against Escherichia coli, Staphylococcus aureus and antifungal activity against Candida albicans using the cup-plate method.

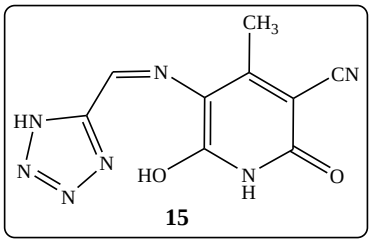


Klapotke T. M. et al[74] have reported the synthesis of 1, 10-azobis (tetrazole) **(14)** by the reaction of 1-aminotetrazole **(13)** with acidic sodium dichloroisocyanurate. The formation of product, a rare chain of 10 nitrogen atoms, has been confirmed by X-ray crystallography. The title compound possesses both exceedingly high explosive performance and sensitivity.



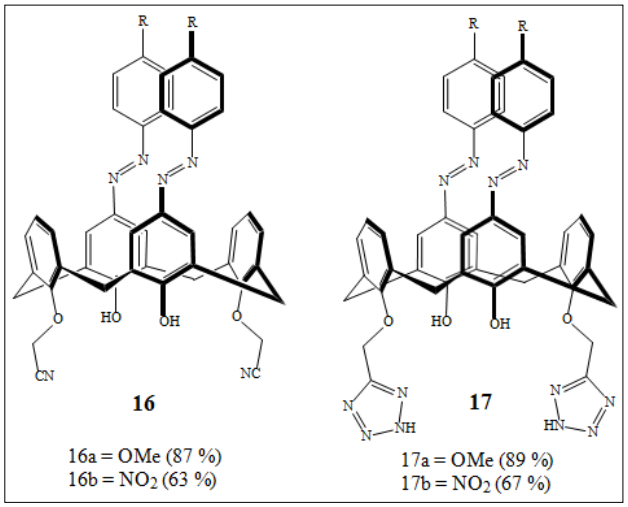
Scheme 4.4: Synthesis of 1, 10-azobis (tetrazole)

Eyduran F. et al[75] have reported the synthesis of some new pyridone dyes **(15)** by coupling 3-cyano-4-methyl-6-hydroxy-2(1H)-pyridone with diazotized 2-amino-5-nitro-1, 3-thiazole, 2-amino-1, 3-thiadiazole, 2-amino-1, 3, 4-triazole, 5-amino-1H-tetrazole and 3-amino-5-Methyl-isoxazole in nitrosyl sulphuric acid. The effects of acid-base, temperature, concentration and solvent on visible absorption spectra of these dyes have been studied.

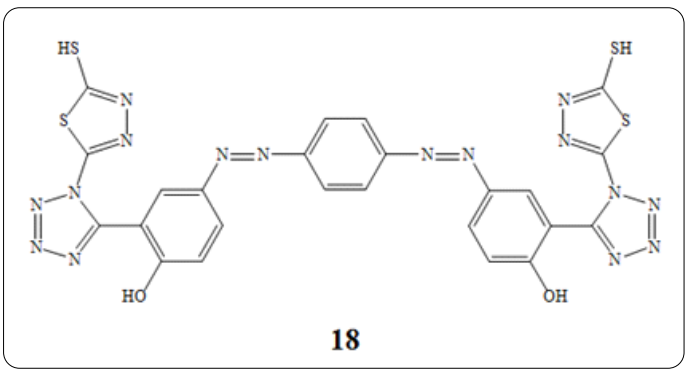


15

Chen Y. -J. et al[76] have reported the synthesis of calix[4]arenes **17a** (R = OMe) and **17b** (R = NO_2) with two distal tetrazole groups at the lower rim and two 4-R phenylazo groups at the upper rim for metal-ion sensing studies. The bisoxymethyltetrazole-modified calix [4] arenes **17a** and **17b** were synthesized by using 1, 3-dipolar cycloaddition of oxyacetonitrile azocalix [4] arenes **16a** and **16b** activated with trimethylsilyl azide. UV/Visible screening illustrates that calix [4] arene **17a** (R = OMe) showed a large bathochromic shift toward Ca^{2+} with good selectivity, whereas **17b** (R = NO_2) showed color changes toward Ca^{2+}, Ba^{2+}, and Pb^{2+}. Calix [4] arenes **17a** and **17b** with two *p*-substituted phenylazo groups at the upper rim and two oxymethyltetrazole groups at the lower rim showed very similar chromogenic sensing abilities toward metal ions.

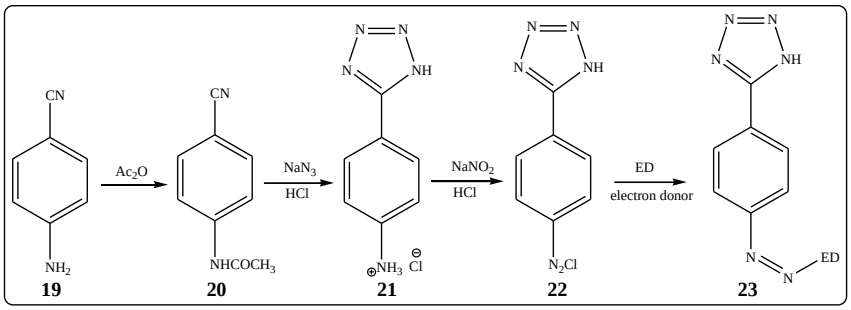


Abood Z. H.[77] has reported the synthesis of two bis - 1, 5-disubstituted tetrazoles compounds having benzothiazole or thiadiazole moiety containing two azo groups **(18)** by reacting corresponding Schiff bases with sodium azide in tetrahydrofuran.



18

Pesyan N. N. et al[78] have reported the synthesis of a series of new tetrazolic azo dyes **(23)** based on (thio)barbiturate and electron-rich aromatics in excellent yield. 4'-cyanoacetanilide **(20)** has been prepared by acylation using acetic anhydride which reacts with sodium azide in presence of HCl to give 4-(1-*H*-tetrazolyl)-aniline.hydrochloride **(21)**. The compound on diazotization followed by reaction with thio barbiturate gives tetrazolic azo dye **(23)**. The antibacterial activity of the synthesized compounds have been tested against gram-positive and gram-negative bacterial strains, namely *A. calcoaceticus*, *E. coli*, *P. aeruginosa*, and *S. aureus*. Some of the synthesized compounds show potential antimicrobial activity.



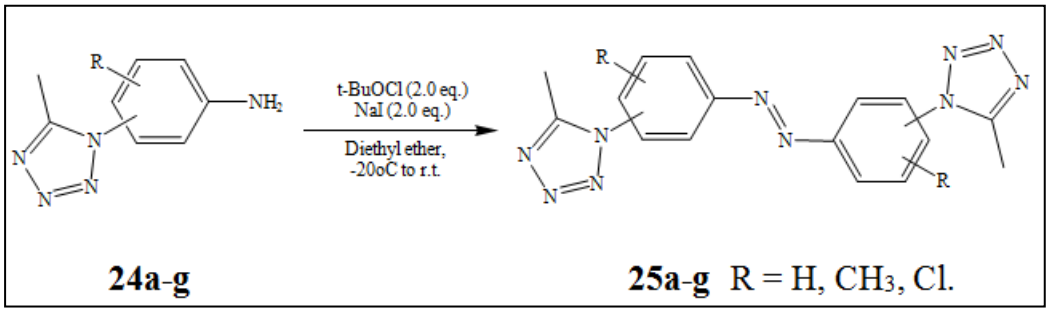
Scheme 4.5: Synthesis of barbiturate-tetrazolic azo dyes

4.3 Present Work

Due to the high potency of the biological applications of tetrazole and high intensity of azo compounds as dyes, herein, we have been designed the scheme for the new symmetrical diazo compounds containing 1, 5-disubstituted tetrazoles moiety. To the best of our knowledge, there is no work on record concerning the synthesis of the new substituted 1, 2-bis(4-(5-methyl-1*H*-tetrazol-1-yl)phenyl)diazenes. In the present research work, we have designed the synthesis of substituted 1, 2-bis(4-(5-methyl-1*H*-tetrazol-1- yl)phenyl)diazenes from 5-methyl-1*H*-tetrazol-1-yl-benzenamine and substituted 5- methyl-1*H*-tetrazol-1-yl-benzenamines.

The structures of the synthesized compounds were established by IR, ^{1}H NMR, ^{13}C NMR and melting point analysis.

Reaction Scheme



Scheme 4.6: Synthesis of 1, 2-Bis(4-(5-methyl-1*H*-tetrazol-1-yl)phenyl)diazenes

4.4 Result and Discussion

4-(5-Methyl-1*H*-tetrazol-1-yl) benzenamine **(24a)** undergo oxidative dimerization by *tert*-butyl hypoiodite in diethyl ether to give symmetrical azobenzene containing two 1, 5-disubstituted tetrazole rings. In this reaction, diphenylhydrazine derivative is formed as an intermediate which is not stable and undergo further oxidation to form azobenzene under the same reaction conditions. Several reaction conditions were investigated to improve the yield of symmetrical azobenzene having 1, 5-disubstituted ring. Various reported methods were applied for the synthesis to improve the reaction conditions and suitable oxidizing agents are also used to optimize the reaction to improve the yield of product. We found that the use of *tert*-butyl hypoiodite as an oxidizing agent for this reaction is found to give excellent yield (93 %).

Table 4.1 Synthesis of 1, 2-bis(4-(5-methyl-1*H*-tetrazol-1-yl)phenyl)diazenes

Product	Molecular Formula	Molecular Weight	Time (hr)	Yield (%)	mp (ºC)
25a	$C_{16}H_{14}N_{10}$	346	3	91	200-201
25b	$C_{16}H_{14}N_{10}$	346	3.5	88	187-189
25c	$C_{16}H_{14}N_{10}$	346	5	82	122-124
25d	$C_{18}H_{18}N_{10}$	374	4	90	147-149
25e	$C_{18}H_{18}N_{10}$	374	4.5	81	168-170
25f	$C_{18}H_{18}N_{10}$	374	4.5	80	106-108
25g	$C_{16}H_{12}Cl_2N_{10}$	414	4	73	95-97

To explore the scope of the synthesis of substituted 1, 2-bis-[4-(5-methyl-1*H*- tetrazol-1-yl)phenyl]diazenes **(25a)**, the same reaction conditions were applied on various 1, 5-disubstituted tetrazole containing anilines using a mixture of *tert*-butyl hypochlorite and sodium iodide in diethyl ether as an oxidizing agent. The results are listed in Table **4.2**. When the substituent 1, 5-disubstituted tetrazole ring is at *meta*- or *para*- position to the amine group in substrate, the yields of products are 85-93%, whereas if 1, 5- disubstituted tetrazole ring is present *ortho*- to the amine group, the yields of azo compounds are 72-80%. It shows that steric hindrance has an effect on the formation of azo compounds.

As depicted in the Scheme **4.6**, 1, 2 - bis(4-(5-methyl-1*H*-tetrazol-1-yl)phenyl) diazenes, azo dyes were synthesized by a multi-step reaction sequence. Step-1 shows the synthesis of substituted 5-Methyl-1-(4-nitrophenyl)-1*H*-tetrazoles were prepared from substituted nitro acetanilides using NaN_3 in presence of $TiCl_4$ in acetonitrile (Chapter II). 4-(5-Methyl-1*H*-tetrazol-1-yl)benzenamine was prepared by reducing the substituted 5- Methyl-1-(4-nitrophenyl)-1*H*-tetrazoles with $NaBH_4$ in presence of $Ni(OAc)_2$ (Step-II, Chapter-3). The 1, 5-disubstituted tetrazole containing anilines on partial oxidation using *tert*-butyl hypochlorite and sodium iodide gives symmetrical azo dyes in good to excellent yield. The compounds were purified by

recrystalization using aqueous ethanol. The purity of the compounds was checked by TLC. Finally the structure of compound was confirmed by ^{1}H NMR, ^{13}C NMR and IR techniques.

The IR spectra of compound (**25a**) showed absorption peak at 3078 cm^{-1} for (=C- H aromatic) stretching and 2941 cm^{-1} for aliphatic C-H stretching; 1587 cm-1 for (C=N) and 1527 cm^{-1} for (N=N) stretching, and 1491cm^{-1} for tetrazole ring. The ^{1}H-NMR spectrum revealed a singlet at δ 2.09 due to protons of $–CH_3$ group present on tetrazole ring and two multiplets at δ 8.18 and 8.26 due to aromatic proton. The IR spectrum of compound 25(a-f) showed absorption at 2850-3100 cm^{-1} attributed to aliphatic and aromatic protons, 1500-1600 cm^{-1} due to N=N, absorption at 900-1050 cm-1 assigned to stretching absorptions of C-N groups. Yield, melting point and molecular formula of the 1, 5-disubstituted tetrazole containing symmetrical azo dyes are given in Table 1. The IR and ^{1}H NMR data was found in good agreement with the newly synthesized compounds.

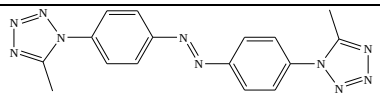
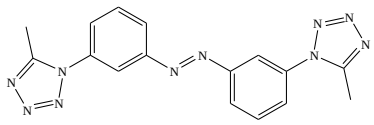
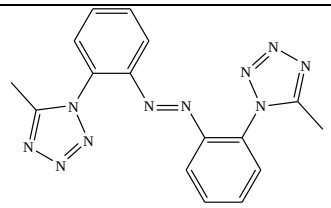
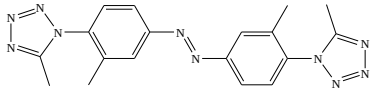
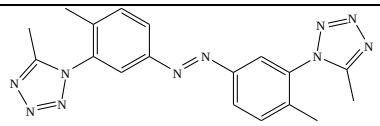
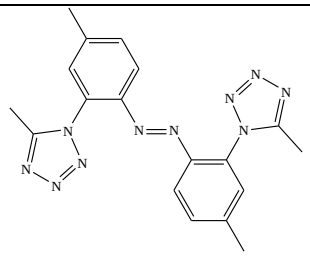
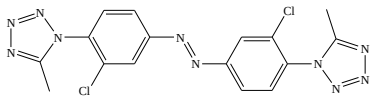
Table 4.2 IR absorption frequencies of 1, 2-bis(4-(5-methyl-1*H*-tetrazol-1-yl)phenyl)diazenes

Product	-N=N- diazo	C=N	Tetrazolyl ring absorption		
			N=N	N-N=N	Tetrazole ring
25a	1527	1610	1485	1288	1116, 1095
25b	1510	1634	1470	1279	1121, 1092
25c	1513	1630	1481	1284	1109, 1080
25d	1508	1622	1478	1288	1118, 1081
25e	1530	1620	1477	1293	1101, 1085
25f	1528	1631	1471	1280	1132, 1099
25g	1551	1644	1491	1278	1146, 1072

Similar types of observations are found in case of other synthesized 1, 5- disubstituted tetrazole containing azobenzenes.

Furthermore, the evidence for the formation of the substituted 1, 5-disubstituted tetrazoles **(22a-g)** were obtained from the ^{1}H NMR and ^{13}C NMR spectra which proved to be the diagnostic tool for the positional elucidation of the proton and carbon atoms respectively.[19] Table **3.5** given below presents the data of chemical shifts of proton in the ^{1}H-NMR spectra of 1, 5-disubstituted tetrazoles.

Table 4.3: ^{1}H NMR Chemical Shifts of 1, 2-bis(4-(5-methyl-1*H*-tetrazol-1-yl) phenyl)diazenes

Entry	Compound	Chemical Shifts (δ ppm)		
		H(Ar)	-CH_3 (tetrazole)(s)	-CH_3 (Ar)(s)
25a		8.26 (d, 4H) 8.19 (d, 4H)	2.09	---
25b		7.79-7.81 (m, 1H), 7.74-7.76 (m, 1H), 7.41-7.43 (m, 1H), 7.29-7.31 (m, 1H).	2.13	---
25c		7.56-7.58 (m, 1H), 7.50-7.52 (m, 1H), 7.32-7.34 (m, 1H); 7.24-7.26 (m, 1H)	2.14	---
25d		7.57-7.59 (m, 2H), 7.49-7.51 (m, 2H), 7.19-7.21 (m, 2H)	2.09	2.39
25e		7.68-7.70 (m, 2H), 7.42-7.44 (m, 2H), 7.23-7.25 (m, 2H).	2.11	2.36
25f		7.59-7.61 (m, 2H), 7.36-7.38 (m, 2H), 7.20-7.22 (m, 2H).	2.12	2.32
25g		8.21-8.23 (m, 2H), 8.05-8.07 (m, 2H), 7.88-7.90 (m, 2H).	2.23	2.48

A significant fact of the data given in **Table 3.5** indicates that the aromatic protons were found in the range of δ 7.5 - 8.5. The aromatic protons *ortho* to the tetrazole ring in compound **22b** are found at δ 7.34 whereas the protons *ortho* to the methyl group were found at δ 6.94. This indicates that the benzene protons *ortho* to the tetrazole ring are deshielded by δ 0.16 ppm relative to the protons *ortho* to methyl group. The deshielding effect may be attributed to the presence of methyl group in the first position of tetrazole ring. The deshielding effect increases

when methyl group get replaced by nitro group **22c**. In 1H-NMR spectrum of compound **22c**, the aromatic protons *ortho* to the tetrazole ring are found at δ 8.17 whereas the protons ortho to the nitro group observed at δ 8.24. Due to the presence of electron withdrawing nitro group, the protons of the benzene ring *ortho* to the nitro group are deshielded by δ 0.07 ppm relative to the protons *ortho* to tetrazole ring. The deshielding effect may be attributed due the presence of methyl group in the first position of tetrazole ring and nitro group as well.

The analogous observations are found for the other synthesized compounds. Hence, the ^{1}H NMR spectra of the synthesized compounds lend convincing evidence to the assigned structure. Similar type of observations was reported previously for the tetrazole containing aromatic compounds.[20]

All of the above observations reveal the presence of 1, 5-disubstituted tetrazole moiety present in the newly synthesized compounds.

4.5 Experimental

1, 5-Disubstituted tetrazole containing anilines were synthesized in our laboratory. All the chemicals used were of AR grade and were purchased from sd-Fine chemicals. The melting points were determined in open capillaries using melting point apparatus (Model MP-96) and were uncorrected. The progress of reaction and purity of the product were monitored by thin layer chromatography using precoated Silica 60/UV_{254} (SDFCL). ^{1}H NMR spectra were recorded in $CDCl_3$ using 400 MHz Varian Mercury plus 400 MHz FT NMR spectrometer. The ^{1}H chemical shift values were reported on δ ppm scale relative to TMS (δ = 0.00 ppm). IR were recorded and reported in cm^{-1}.

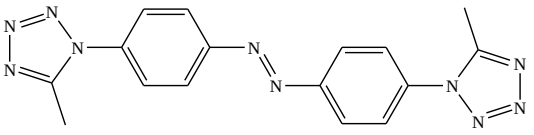
General procedure for the synthesis of 1, 2-bis(4-(5-methyl-1H-tetrazol-1- yl)phenyl)diazenes

To a mixture of 4-(5-methyl-1H-tetrazol-1-yl)benzenamine **24a** (5 mmol.) and NaI (10 mmol,) in diethyl ether (50 ml) was added t-BuOCl (10 mmol,) under N_2 atmosphere at room temperature. The mixture was stirred for 3 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with aqueous $Na_2S_2O_3$ (1M, 50 ml), and the solution was extracted with CH_2Cl_2 (75ml * 3). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum to give the crude product. The product was purified by recrystalization using aqueous ethanol. The yield of the product was 91%.

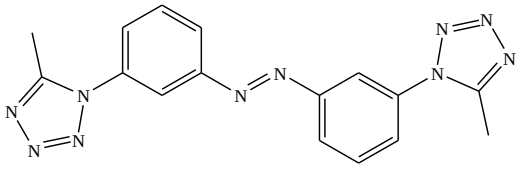
All the other compounds were synthesized by using same procedure given above. The synthesized compounds, listed in **Table. 4.1** were characterized by IR, ^{1}H-NMR and ^{13}C-NMR.

1, 2-bis(4-(5-methyl-1H-tetrazol-1-yl) phenyl)diazenes (25a)

^{1}H NMR ($CDCl_3$): δ 8.19 (d, 4H), 8.26 (d, 4H); 2.09 (s, 6H). **IR (KBr, cm-1)**: 3097, 3078, 2941, 2870, 1610, 1587, 1527, 1485, 1410, 1346, 1288, 1116, 1095, 995, 912, 871, 813, 746.

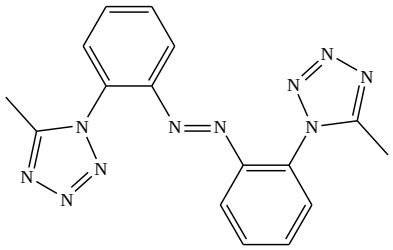


1, 2-bis(3-(5-methyl-1H-tetrazol-1-yl) phenyl)diazenes (25b)



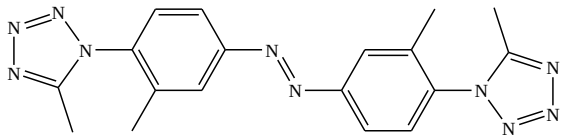
^{1}H NMR ($CDCl_3$): δ 7.79-7.81 (m, 2H), 7.74-7.76 (m, 2H), 7.41-7.43 (m, 2H), 7.29-7.31 (m, 2H), 2.13 (s, 6H). **IR (KBr, cm^{-1})**: 3080, 2997, 1614, 1583, 1527, 1496, 1435, 1354, 1298, 1109, 1080, 1030, 910, 842, 806, 752.

1, 2-bis(2-(5-methyl-1H-tetrazol-1-yl)phenyl)diazenes (25c)



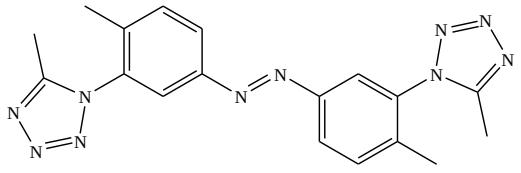
^{1}H NMR ($CDCl_3$): δ 7.56-7.58 (m, 2H), 7.50-7.52 (m, 2H), 7.32-7.34 (m, 2H), 7.24-7.26 (m, 2H), 2.14 (s, 6H). **IR (KBr, cm^{-1})**: 3092, 2968, 1630, 1577, 1513, 1481, 1423, 1359, 1284, 1109, 1080, 1004, 917, 857, 821, 762, 693.

1, 2-bis(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)diazenes (25d)



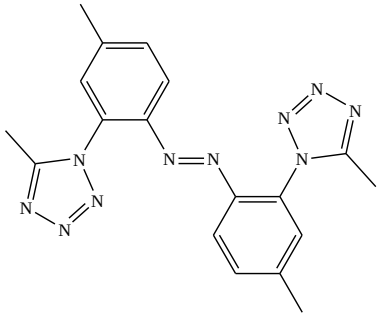
^{1}H NMR ($CDCl_3$): δ 7.57-7.59 (m, 2H), 7.49-7.51 (m, 2H), 7.19-7.21 (m, 2H), 2.39 (s, 6H), 2.09 (s, 6H). IR (KBr, cm^{-1}): 3088, 3066, 2976, 2854, 1621, 1580, 1519, 1472, 1417, 1376, 1297, 1129, 1094, 990, 917, 860, 810, 742.

1, 2-Bis(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)diazenes (25e)



^{1}H NMR ($CDCl_3$): δ 7.68-7.70 (m, 2H), 7.42-7.44 (m, 2H), 7.23-7.25 (m, 2H), 2.46 (s, 6H), 2.17 (s, 6H). IR (KBr, cm^{-1}): 3100, 3058, 2961, 2849, 1622, 1589, 1508, 1478, 1411, 1350, 1288, 1118, 1081, 990, 916, 870, 810, 756.

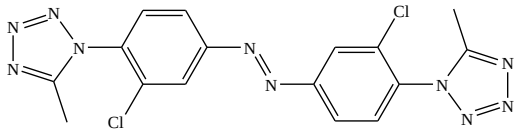
1, 2-Bis(4-methyl-2-(5-methyl-1H-tetrazol-1-yl)phenyl)diazenes (25f)



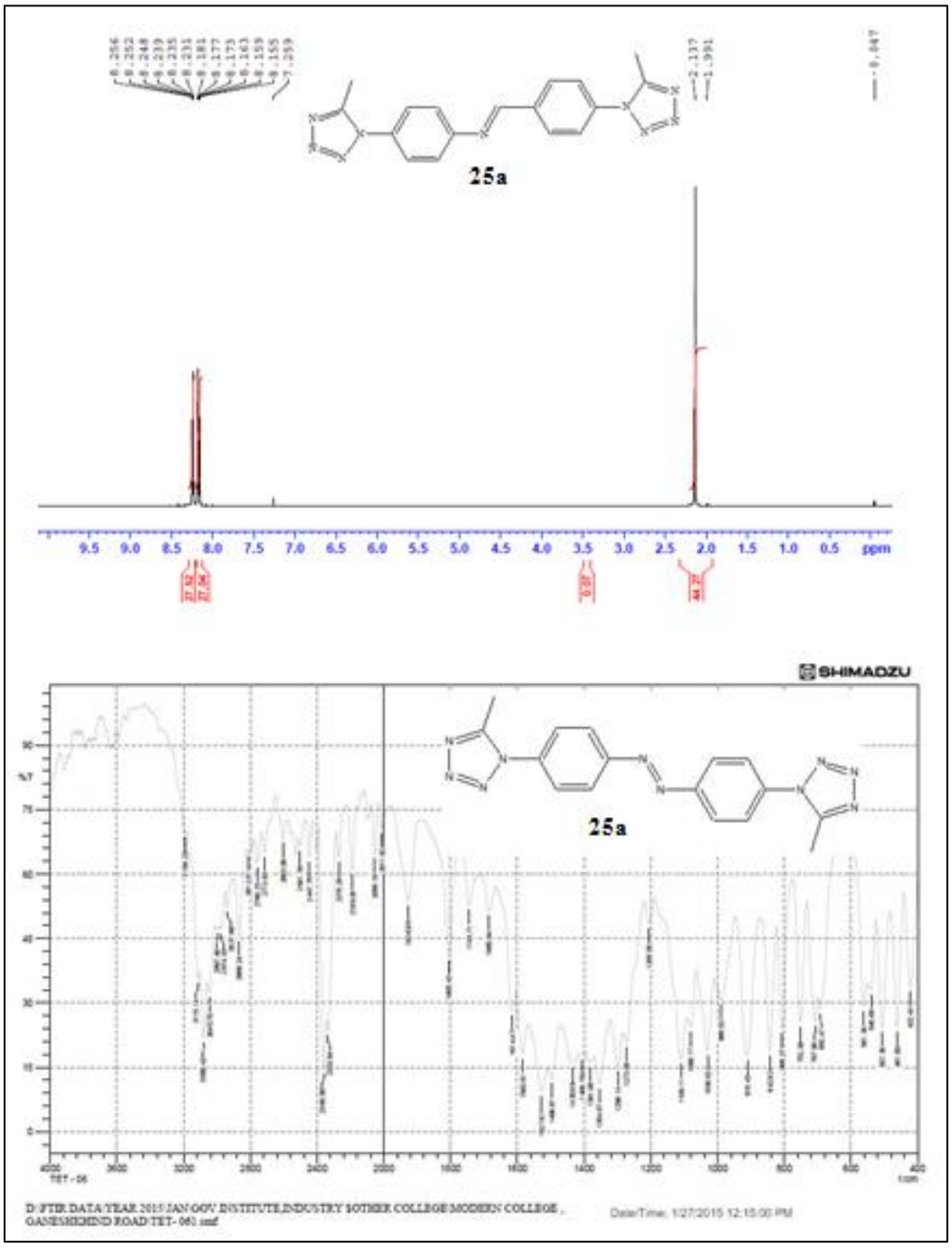
^{1}H NMR ($CDCl_3$): δ 7.59-7.61 (m, 2H), 7.36-7.38 (m, 2H), 7.20-7.22 (m, 2H), 2.47 (s, 6H), 2.08 (s, 6H). **IR (KBr, cm^{-1})**: 3112, 2972, 1600, 1574, 1519, 1491, 1412, 1339, 1274, 1129, 1089, 999, 919, 860, 819, 751, 697.

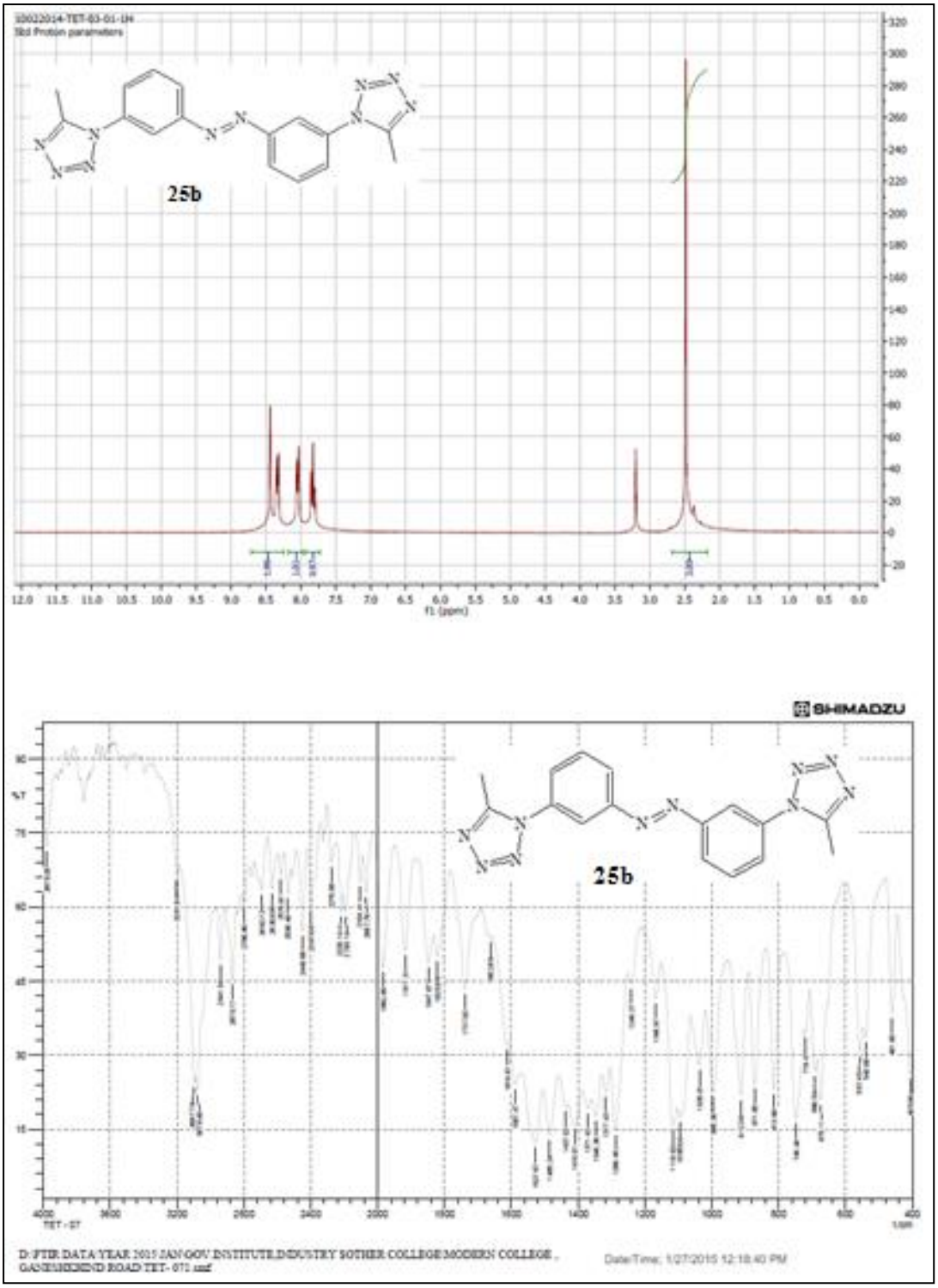
1, 2-bis(3-chloro-4-(5-methyl-1H-tetrazol-1-yl)phenyl)diazenes (25g)

^{1}H NMR ($CDCl_3$): δ 8.21-8.23 (m, 2H), 8.05-8.07 (m, 2H), 7.88-7.90 (m, 2H), 2.49 (s, 6H), 2.23 (s, 6H). **IR (KBr, cm^{-1})**: 3088, 3066, 2976, 2854, 1621, 1580, 1519, 1472, 1417, 1376, 1297, 1129, 1094, 990, 917, 860, 810, 742.



Selected Spectra





4.6 Conclusion

The interest has made in the synthesis of 1, 5-disubstituted tetrazoles due to its high potency of the biological applications of tetrazole scaffolds. Herein, we have described the synthesis of the novel symmetrical diazo compounds containing two 1, 5- disubstituted tetrazole nuclei.

In the present research work, we have designed and synthesized for the first time 1, 2-bis(4-(5-methyl-1H-tetrazol-1-yl)phenyl)diazenes from the corresponding 5-methyl- 1H-tetrazol-

1-yl-benzenamines by using previously reported method. In this method, 5- Methyl-1H-tetrazol-1-yl-benzenamines **(24a-g)** undergo oxidative dimerization by t- BuOCl in presence of NaI in diethyl ether to give diazo compounds **(25a-g)** in good to excellent yields. The structures of the synthesized compounds were established by IR, ^{1}H NMR and melting point analysis.

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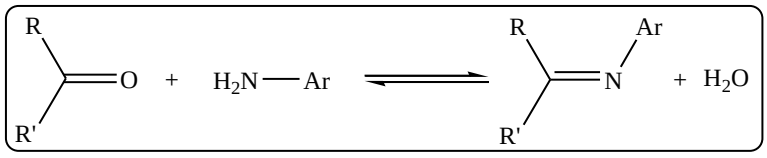
CHAPTER 5
SYNTHESIS OF SCHIFF BASES OF SUBSTITUTED (5-METHYL-1*H*-TETRAZOL-1-YL)BENZENAMINES

Introduction:

Schiff bases, named after Hugo Schiff[1] (1864), are the condensation compounds containing an azomethine group (-CH=N-). They are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases in a broad sense have the general formula $R^1R^2C=NR^3$, where R^1 and R^2 represent hydrogen, an alkyl or an aryl and R^3 an alkyl or aryl group. Schiff bases of aromatic aldehydes with effective conjugation system are more stable than the aliphatic aldehydes. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerisable.[2]

In general, due to the less steric hindrance, aldehydes react faster than ketones in condensation reactions with aromatic amines leading to the formation of Schiff bases. Furthermore, the extra carbon of ketone donates electron density to the carbonyl carbon and thus makes the ketone less electrophilic as compared to aldehydes.[3]



R, R' = H, alkyl, aryl

Schiff bases are crystalline or oily in nature, insoluble in water but soluble in organic solvents. They are weak bases, forming salts with acids in an anhydrous medium; in aqueous acid solutions they undergo hydrolysis to yield an amine and aldehyde. Schiff bases undergo hydrogenation to give secondary amines (RR ′CH-NHR″). Schiff bases are mostly used as intermediates because they show cycloaddition reaction with compounds such as thioglycolic acid, NaN_3, chloroacetyl chloride etc. resulting in thiazolidinone, tetrazole, azetidinone, etc. respectively. Therefore Schiff bases are important scaffolds in the synthesis of numerous biologically active heterocyclic compounds.

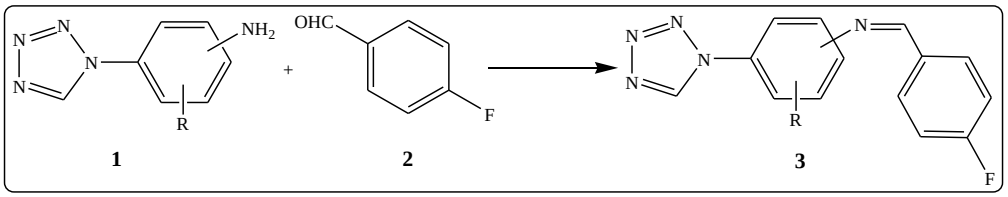
Schiff bases are some of the most widely used organic compounds. They have a wide range of applications such as catalysts, dyes, pigments, polymer stabilizers and intermediates in organic synthesis. Schiff bases comprising bi or tri dentate ligands are capable of forming very stable complexes with transition metals. It is also interesting to note that Schiff bases are important intermediates in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. Schiff bases have also been shown to exhibit a broad range of biological activities including antimicrobial, [4] anti-bacterial, [5] antifungal, [6] anti-

inflammatory, [7] analgesic, [8] anti- tubercular, [9] anticancer, [10] anti-HIV, [11] antiparasitic, [12] antioxidant, [13] and diuretics.[14]

5.1 Literature Survey

In spite of huge focus in the synthesis and creation of new pharmaceutical products of 1, 5-disubstituted tetrazoles, surprisingly, a Sci-Finder® and CrossFire® survey revealed that only one synthetic analogous strategy has been reported for the preparation of Schiff bases by the condensation of various (1*H*-tetrazol-1-yl)benzenamine with 4-fluorobenzaldehyde (Scheme **5.1**). Apart from it, a Sci-Finder® and CrossFire® survey shows that only one approach has reported on correlation between the rates of benzylidene condensation of R-tetrazol-1-ylphenylamines and their dissociation constants. Till day, no any strategy has been reported for the preparation of Schiff bases from (5-methyl-1*H*-tetrazol-1-yl)benzenamine and substituted (5-methyl-1*H*-tetrazol-1- yl)benzenamines.

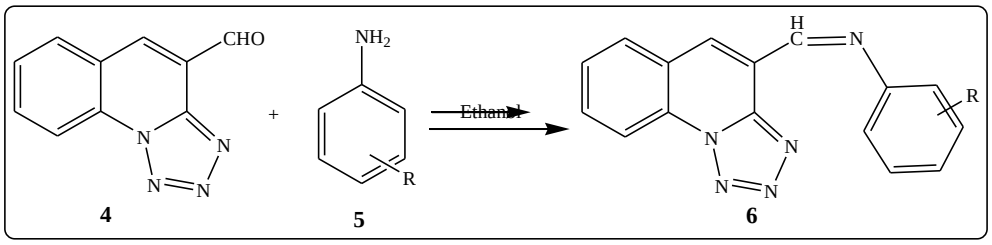
Pavlov A.V. et al[15] have reported, for the first time, the synthesis of Schiff bases **(3)** from (1*H*-tetrazol-1-yl)benzenamine **(1)** and its derivatives by the condensation with 4-fluorobenzaldehyde in alcohol (Scheme **5.1**).



Scheme 5.1: Synthesis of Schiff bases containing substituted 1-*H*-tetrazole

Furthermore, *Pavlov A.V. et al*[16] have reported the correlation between the logarithm of the rate constant of the condensation of 4-fluorobenzaldehyde with R- tetrazol-1-ylphenylamines and their pK_{BH}+ values. The reaction constant ρ in the Hammett equation has been determined.

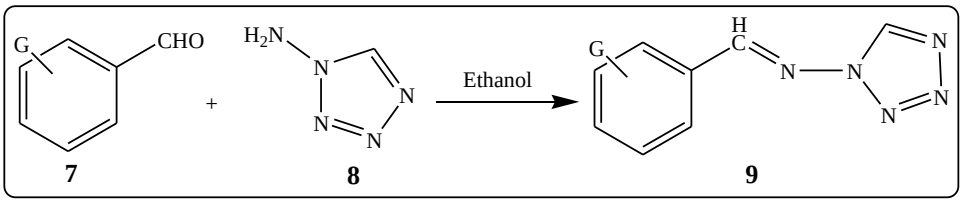
In the synthesis of, potentially active antimicrobial agents, quinoline based azetidinone and thiazolidinone analogues, *Mistry B. and Jauhari S.*[17] have reported the synthesis of Schiff base **(6)** by refluxing tetrazolo[1, 5-1]quinoline-4-carbaldehyde with aromatic amines in ethanol (Scheme **5.2**).



Scheme 5.2: Synthesis of Schiff bases of tetrazolo[1, 5-1]quinoline-4-carbaldehyde

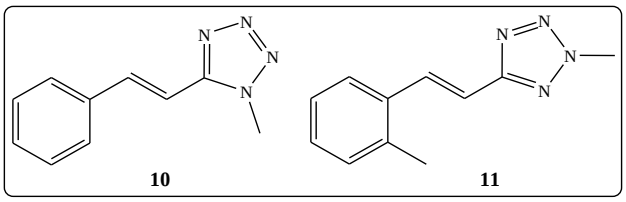
Nitrogen containing heterocyclics are one of the most extensively synthesized and screened compounds as they show diverse pharmacological activities. *Jamal M.Y et al*[18] have reported the synthesis of a new series of Schiff's bases fused with tetrazole ring namely N-

(substituted benzylidene)-2-amino tetrazole **(9)** through the reaction of 2-amino tetrazole with substituted benzaldehydes (Scheme **5.3**). The antioxidant properties of the prepared compounds were measured using the metal ions (Fe^{+3}, Cu^{+2}), the ferrozine and 2, 9-dimethyl-1, 10-phenanthroline.

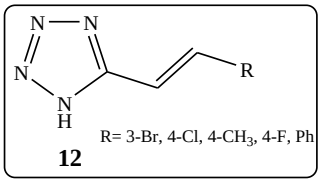


Scheme 5.3: Synthesis of Schiff bases of 2-amino tetrazole

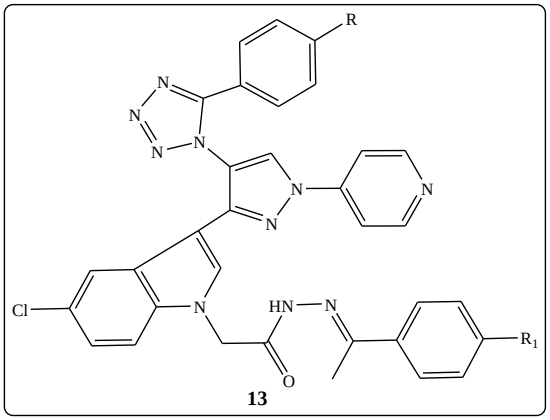
Degtyarik M.M. et al[19] have reported that Schiff bases, 2-([1-methyl-1*H*-tetrazol- 5-ylimino]-methyl)-phenol **(10)** and 2-([2-methyl-1*H*-tetrazol-5-ylimino]-methyl)-phenol **(11)** can be prepared by reaction of salicyaldehyde with corresponding 5-amino-*N*-methyl tetrazole in ethanol under argon. The hydrated cobalt (II), nickel (II) and copper (II) chlorides were found to react with these compounds in EtOH–MeCN or MeOH–MeCN producing corresponding metal complexes.



Kumar K.R. et al[20] have reported the synthesis of thiazol-4-ones containing tetrazole moiety from the corresponding Schiff bases bearing tetrazole moiety. Where, Schiff bases **(12)** were prepared from 5-amino tetrazole by reacting with substituted aromatic aldehydes. The resulting compounds are found to exhibit antibacterial and antifungal activities



During the synthesis of some new indoles having tetrazol - 1, 3, 4 – oxadiazole moiety, *Ashokgajapathiraju P et al*[21] have prepared a Schiff base, 2-(5-chloro-3-(1- (pyridine-4-yl)-4-(1-(4-substituted phenyl)-1*H*-tetrazol-3-yl)-1*H*-Indol-1-yl)-*N*'-(1-(4- substituted phenyl)ethylidene) acetohydrazide **(13)**. The resulting compound showed good antibacterial and good antifungal activity when compared with standard compounds.



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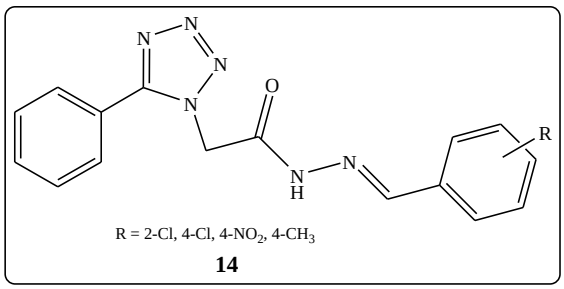
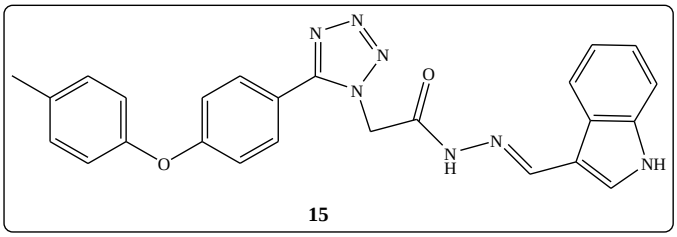
Mohite P.B. et al[22] have prepared a series of tetrazole Schiff bases **(10)** and demonstrated that these compounds possess good antibacterial and antifungal activities when tested by the cup plate method.



14

Patidar A. et al[23] have reported the synthesis of Schiff base *N*-((1*H*-indol-3-yl)methylene)-2-(5-(4-tolyloxy)- phenyl)-1H-tetrazol-1-yl)acetohydrazide **(11)** from 2-{5-[4-(4-methylphenoxy) phenyl]-1*H*-tetrazol-1-yl}acetohydrazide by condensation with indole-3-aldehyde. This Schiff base on treatment with thioglycolic acid gives thiazolidinone.

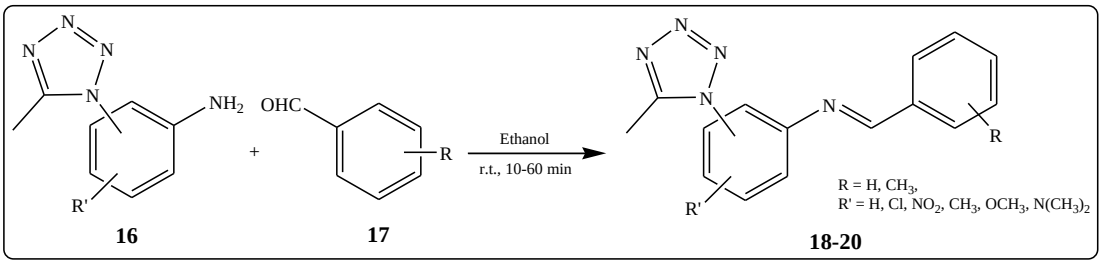


15

5.2 Present work

As 1, 5-disubstituted tetrazole unit are interesting bio–scaffolds, herein, the introduction of this moiety into Schiff bases was carried out to improve the biological activities of these scaffolds. In the present work, we describe the synthesis of a series of some novel Schiff bases containing 1, 5-disubstituted tetrazoles by condensation of 4-(5- Methyl-1*H*-tetrazol-1-yl)benzenamine and substituted 4-(5-Methyl-1*H*-tetrazol-1- yl)benzenamines with aromatic aldehydes in ethanol at room temperature. The structure of all newly synthesized compounds was well characterized by their elemental analysis, mass, IR, ^{1}H-NMR and ^{13}C-NMR spectral data.

Reaction Scheme

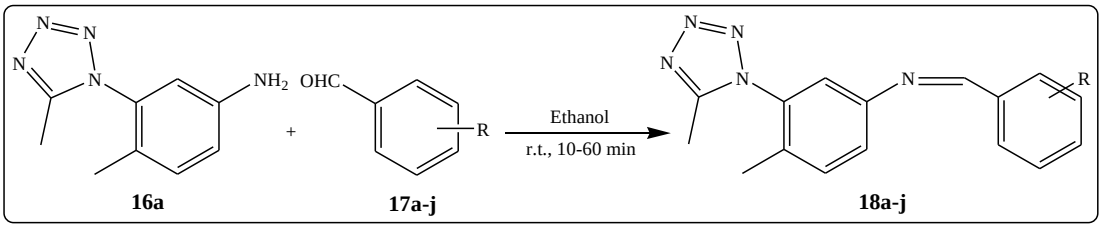


Scheme 5.4: Synthesis of Schiff bases of Substituted (5-Methyl-1*H*-tetrazol-1-yl)benzenamines

5.3 Result and Discussion

Generally, Schiff bases are prepared by the reaction of aliphatic / aromatic primary amines with aliphatic / aromatic aldehydes using acidic catalyst in different solvents at room temperature to reflux conditions.

Table 5.1: Synthesis of Schiff bases of 4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl) benzenamine (18a-j)



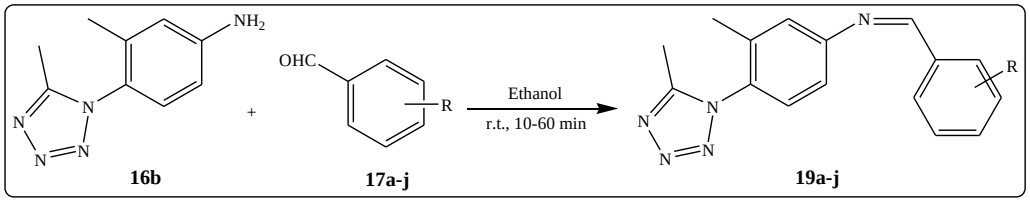
Entry	R	Time (min)	Yield (%)	Melting Point
18a	H	40	95	138-140
18b	4-CH_3	55	90	115-117
18c	4-OCH_3	30	92	143-145
18d	4-Cl	20	97	177-179
18e	3-Cl	20	95	141-143
18f	2-Cl	25	91	123-125
18g	4-NO_2	10	98	215-217
18h	3-NO_2	20	96	108-110
18i	2-NO_2	30	93	125-127
18j	4-$N(CH_3)_2$	20	89	136-137

In the present work, three series of novel Schiff bases namely, i) *N*- benzylidene-4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl)benzenamines **(18a-j)**, ii) *N*-benzylidene-3-methyl-4-(5-methyl-1*H*-tetrazol-1-yl)benzenamines **(19a-j)** and iii) *N*-benzylidene-4-(5-methyl-1*H*-tetrazol-1-yl)benzenamines **(20a-j)** were synthesized by condensing different aromatic aldehydes with 4-methyl-3-(5-methyl-1*H*- tetrazol-1-yl)benzenamine (**16a**), 3-methyl-4-(5-methyl-1*H*-tetrazol-1-

yl)benzenamine **(16b)** and 4-(5-methyl-1*H*-tetrazol-1-yl)benzenamine **(16c)** respectively. Compound **(18h)** was synthesized by stirring 4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl)benzenamine **(16a)** with 4-nitrobenzaldehyde **(17h)**. The reaction was carried out in ethanol at room temperature. The progress of reaction was monitored by TLC where it was found that the reaction was completed within 10 min.

These newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and IR spectral analysis.

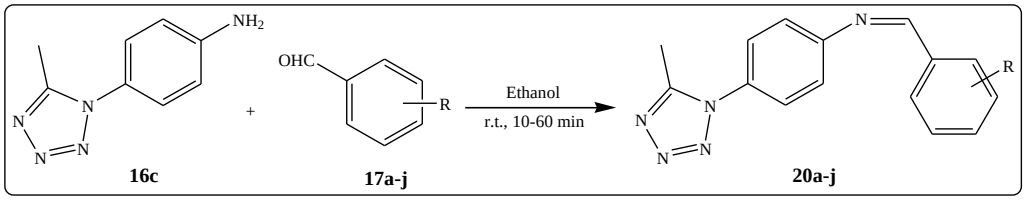
Table 5.2 Synthesis of Schiff bases of 3-methyl-4-(5-methyl-1*H*-tetrazol-1-yl) benzenamine (19a-j)



Entry	R	Time (min)	Yield (%)	Melting Point
19a	H	35	94	132-134
19b	4-CH_3	50	89	148-150
19c	4-OCH_3	30	91	146-148
19d	4-Cl	20	95	120-122
19e	3-Cl	50	93	131-133
19f	2-Cl	55	92	138-140
19g	4-NO_2	10	97	172-174
19h	3-NO_2	20	93	184-186
19i	2-NO_2	50	93	168-170
19j	4-$N(CH_3)_2$	60	90	149-151

The formation of (Benzylidene) (4-(5-methyl-1*H*-tetrazol-1-yl)phenyl)amines were confirmed by recording their ^{1}H NMR, ^{13}C NMR, IR and mass spectra. IR spectrum of compound (**16h)** showed absorption at 1599 which is due to the C=N (azomethine) stretching. Absorption band at 1508 cm-1 is due to N=N of tetrazole ring. The ^{1}H-NMR of spectrum of (**16h)** showed two singlets at δ 2.11 and δ 2.52, which are due to two –CH_3 groups present on tetrazole and phenyl ring respectively. Seven peaks observed in the region of δ 7.18-8.30 indicate the presence of seven different aromatic protons. Similarly a singlet at δ 9.00 is due to a proton of azomethine group. The ^{13}C NMR spectrum of (**18h)** showed sixteen peaks which confirm the presence of sixteen carbon atoms present in the molecule. The relative positions of these peaks also confirm the structure of the compound. Finally, the mass spectrum of compound (**18h)** showed the molecular ion peak at *m/z* 322, which is in agreement with the molecular formula $C_{16}H_{14}N_6O_2$.

Table 5.3: Synthesis of Schiff bases of 4-(5-methyl-1*H*-tetrazol-1-yl) benzenamine (20a-j)



Entry	R	Time (min)	Yield (%)	Melting Point
20a	H	40	95	139-141
20b	4-CH_3	55	90	154-156
20c	4-OCH_3	30	92	141-143
20d	4-Cl	20	97	142-144
20e	3-Cl	15	95	191-193
20f	2-Cl	25	91	128-130
20g	4-NO_2	15	98	191-193
20h	3-NO_2	20	96	156-158
20i	2-NO_2	35	93	172-174
20j	4-$N(CH_3)_2$	45	89	152-154

The characteristic absorption frequencies of the newly synthesized Schiff bases **(18a-j) are** presented in the **Table 5.4.**

Table 5.4 Characteristic absorption frequencies of the novel Schiff bases (18a-j)

Entry	– HC=N-, (azomethine) (cm^{-1})	C=N, (tetrazolyl) (cm^{-1})	N=N, Frequency (cm^{-1})	N-N=N, Frequency (cm^{-1})	Tetrazole ring, Frequency (cm^{-1})
18a	1642	1602	1499	1294	1110, 1082
18b	1634	1600	1513	1282	1119, 1077
18c	1630	1584	1491	1276	1123, 1079
18d	1621	1592	1498	1281	1098, 1072
18e	1626	1588	1495	1281	1126, 1073
18f	1629	1598	1509	1274	1120, 1059
18g	1631	1587	1485	1288	1102, 1051
18h	1631	1611	1490	1299	1101, 1078
18i	1628	1581	1508	1305	1102, 1089
18j	1625	1584	1501	1299	1106, 1080

The IR data of C=N (azomethine) stretching frequencies of Schiff bases **18a-j** synthesized, in the present work, from 4-methyl-3-(5-methyl-1*H*-tetrazol-1- yl)benzenamine

(**16a**) are summarized in Table **5.4**. All the newly synthesized Schiff bases **18a-j** gave absorption band in the range 1620-1650 cm^{-1} indicate the presence of the C=N (azomethine) group. These values are in agreement with the values reported in literature.

Table **5.4** illustrates the IR data of C=N stretching frequencies of tetrazole ring present in the compounds **18a-j** synthesized in the present work. From the table, it is evident that all the newly synthesized tetrazole containing Schiff bases **18a-j** gave an absorption band in the range 1580-1610 cm^{-1} indicate the presence of the C=N functional group of tetrazole ring. The IR spectral values obtained for C=N bond of tetrazole ring in the present work are in agreement with the values reported in literature.[24]

The absorption bands for the N=N functional group of the newly synthesized 1, 5-disubstituted tetrazoles (**18a-j)** are also presented in the Table **5.4**. All the newly synthesized compounds showed an absorption band between 1480-1520 cm^{-1}, which confirms the presence of N=N group of tetrazole ring. These values are in agreement with the values reported in literature.[25]

Furthermore, the appearance of an absorption band around 1250-1300 cm^{-1} reveals the presence of N-N=N in the molecule. In the present work, similar observations are found with regard to the presence N-N=N linkage of tetrazole ring. The IR absorptions at 1294 cm^{-1}, 1282 cm^{-1}, 1276 cm^{-1}, 1281 cm^{-1}, 1281 cm^{-1}, 1274 cm^{-1}, 1288 cm^{-1}, 1299 cm^{-1}, 1305 and 1299 $cm^{-1}$are due to the presence of N-N=N functional groups present in the compounds **(18a-j)**. **Table 5.4** presents the data of tetrazole ring frequencies of the newly synthesized compounds **(18a-j**). These values are also in accordance with the values of tetrazole ring reported in litetrature.[26]

The presence of C-Cl linkage in the compound **18d, 18e** and **18f** is confirmed by the presence of absorption bands at 762 cm^{-1}, 754 cm^{-1} and 751 cm^{-1} respectively. All of the above observations reveal the presence of tetrazole moiety along with azomethine group in the newly synthesized compounds.

Furthermore, the evidences for the formation of the substituted Benzylidene-(4- methyl-3-(5-methyl-tetrazol-1-yl)phenyl)amine**s (18a-j)** were obtained from ^{1}H NMR and ^{13}C NMR spectra which proved to be the diagnostic tool for the positional elucidation of the proton and carbon atoms respectively.[27] Table **5.5** given below presents the data of chemical shifts of proton in the ^{1}H NMR spectra of substituted benzylidene-(4-methyl-3-(5-methyl-tetrazol-1- yl)phenyl) amines.

A significant fact of the data given in the Table **5.5** indicates that all the compounds **18a-j** show a signal in the range of δ 8.00 – 9.00 for azomethine (N=CH) proton. Similar types of observations were reported previously for the azomethine group of Schiff bases.

All the synthesized compounds in this work show a singlet in the range of δ 2.06 – 2.11 for three protons of methyl group present on tetrazole ring. ^{1}H NMR spectra of Schiff bases

show singlet in the range of δ 2.50 for methyl group present on aromatic ring. As expected the aromatic protons were found in the range of δ 6.74 – 8.77. All of the above observations from ^{1}H-NMR spectra of Schiff bases **18a-j** reveal the structures of all the synthesized compounds.

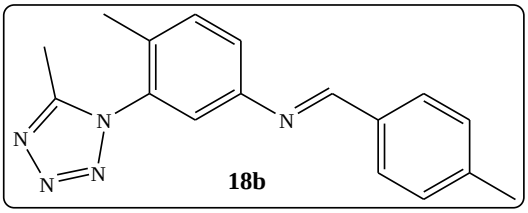
Table 5.5: ^{1}H-NMR chemical shifts of the Schiff bases (18a-j)

Entry	Chemical shift (δ ppm)			
	=CH-	-CH_3 (tetrazole)(s)	-CH_3 (Ar)(s)	-H (Ar)
18a	8.45	2.09	2.51	7.90-7.92 (s, 1H), 7.45-7.54 (m, 5H), 7.38 (d, 1H), 7.11 (s, 1H).
18b	8.45	2.08	2.50, 2.44	7.79 (d, 2H), 7.44 (d, 1H), 7.36 (d, 1H), 7.30 (d, 2H), 7.09 (s, 1H).
18c	8.41	2.07	2.50, 3.90	7.85 (d, 2H), 7.43 (d, 1H), 7.35 (d, 1H), 7.07 (s, 1H), 6.99 (d, 2H).
18d	8.46	2.09	2.51	7.85 (d, 2H), 7.46-7.49 (d, 2H), 7.38 (d, 2H), 7.11 (s, 1H).
18e	8.46	2.11	2.52	7.94-7.96 (m, 1H), 7.75 (d, 1H), 7.49-7.53(m, 3H), 7.37(d, 1H), 7.11(s, 1H)
18f	8.95	2.09	2.51	8.23-8.26 (m, 1H), 7.44-7.47 (m, 3H), 7.39-7.42 (m, 2H), 7.13 (d, 1H).
18g	8.62	2.11	2.52	8.35 (d, 2H), 8.11(d, 2H), 7.52-7.55 (m, 1H), 7.44 (m, 1H), 7.18-7.20 (m, 1H).
18h	8.61	2.10	2.51	8.77 (d, 1H), 8.36 (d, 1H); 8.25 (d, 1H), 7.70 (d, 1H), 7.44 (d, 1H), 7.42 (d, 1H), 7.17 (d, 1H).
18i	9.00	2.11	2.52	8.29 (d, 1H), 8.12 (d, 1H), 7.78-7.80 (m, 1H), 7.69-7.72 (m, 1H), 7.50-7.52 (m, 1H), 7.44-7.46 (m, 1H), 7.19 (d, 1H)
18j	8.34	2.06	2.49	7.76 (d, 2H), 7.41 (d, 1H), 7.35 (d, 1H), 7.06 (d, 1H), 6.74 (d, 2H)

The proton NMR spectrum of the compound, (4-Methylbenzylidene)(4-methyl-3- (5-methyl-1*H*-tetrazol-1-yl)phenyl)amine **(18b)** exhibits a singlet at δ 2.08 due to protons of methyl group present on carbon atom of tetrazole ring. Two singlets were observed at δ 2.44 and δ 2.50 confirm the presence of two methyl groups present on aromatic ring. A doublet observed at δ 7.09 may be assigned to the aromatic proton ortho to the tetrazole ring. A doublet of doublet at δ 7.36 must be due to aromatic proton of the benzene ring ortho to azomethine nitrogen atom. A multiplet at 7.44 can be attributed to the aromatic proton of the phenyl ring *meta* to the tetrazole

ring. A doublet at δ 7.79 can be assigned to the protons of phenyl ring ortho to azomethine carbon atom whereas a double at δ 7.30 can be recognized for two aromatic protons ortho to the methyl group. The singlet observed at δ 8.45 is for azomethine proton.

From all of the above observations of ^{1}H-NMR spectrum of the compound, (4-methylbenzylidene)(4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl)phenyl)amine **(18b)**, the structure of the compound can be predicted as,



18b

The ^{13}C-NMR spectrum of (**18b)** showed fifteen peaks which confirms the presence of fifteen non-equivalent carbon atoms present in the molecule. The observed values are comparable with theoretical values of the above predicted compound. Finally, the mass spectrum of compound (**18h)** showed the molecular ion peak at *m/z* 322, which is in agreement with the molecular formula $C_{16}H_{14}N_6O_2$.

Similar types of observations are found for other synthesized compounds.

5.4 Experimental

1, 5-Disubstituted tetrazole containing anilines were synthesized in our laboratory. All the chemicals used were of AR grade and were purchased from sd-Fine chemicals. The melting points were determined in open capillaries using melting point apparatus (Model MP-96) and were uncorrected. The progress of reaction and purity of the product were monitored by thin layer chromatography using precoated Silica 60/UV_{254} (SDFCL). ^{1}H NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using 400 MHz Varian Mercury plus 400 MHz FT NMR spectrometer. The ^{1}H chemical shift values were reported on δ ppm scale relative to TMS (δ = 0.00 ppm). FT-IR and/or AT-IR spectra were recorded and reported in cm^{-1}.

General Procedure for the synthesis of Schiff bases of 4-methyl-3-(5- methyl-1H-tetrazol-1-yl)benzenamine (18a-j)

A mixture of 4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl)benzenamine 12a (1 mmol, 0.50 g), benzaldehyde (1 mmol, 0.28 g) and 5 ml ethanol was taken in 25 ml round bottom flask. The resultant reaction mixture was stirred for 4 hrs. at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to 5 -10 ^{o}C and solid product was filtered. The product was dried (yield of product: 95 %). The crude product was purified by recrystalization using 50 % aqueous ethanol. The product was characterized by 1H-NMR, 13C-NMR and FTIR technique.

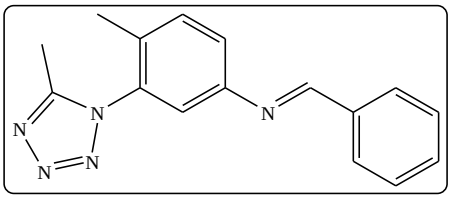
General Procedure for the synthesis of Schiff bases of 4-(5-methyl-1H- tetrazol-1-yl)benzenamine (19a-j)

A mixture of 4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl)benzenamine 12a (1 mmol, 0.50 g), benzaldehyde (1 mmol, 0.28 g) and 5 ml ethanol was taken in 25 ml round bottom flask. The resultant reaction mixture was stirred for 4 hrs. at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to 5 -10 ^{o}C and solid product was filtered. The product was dried (yield of product: 95 %). The crude product was purified by recrystalization using 50 % aqueous ethanol. The product was characterized by ^{1}H NMR, ^{13}C NMR and IR technique.

General Procedure for the synthesis of Schiff bases of 4-methyl-3-(5- methyl-1H-tetrazol-1-yl)benzenamine (20a-g)

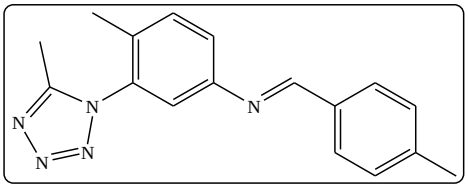
A mixture of 4-methyl-3-(5-methyl-1*H*-tetrazol-1-yl)benzenamine 12a (1 mmol, 0.50 g), benzaldehyde (1 mmol, 0.28 g) and 5 ml ethanol was taken in 25 ml round bottom flask. The resultant reaction mixture was stirred for 4 hrs. at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to 5 -10 ^{o}C and solid product was filtered. The product was dried (yield of product: 95 %). The crude product was purified by recrystalization using 50 % aqueous ethanol. The product was characterized by ^{1}H NMR, ^{13}C NMR and IR technique.

(Benzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18a)



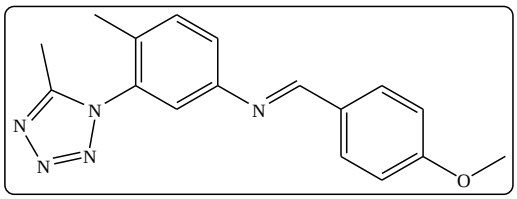
^{1}H-NMR (CDCl$_3$): δ 8.45 (s, 1H), 7.90-7.92 (s, 1H), 7.45-7.54 (m, 5H), 7.38 (d, 1H), 7.11 (s, 1H), 2.51 (s, 3H), 2.09 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 17.0, 119.0, 123.0, 128.0, 129.0, 132.0, 132.3, 132.4, 133.0, 135.0, 151.0, 152.0, 161.0. **IR (KBr, cm^{-1})**: 3043, 2951, 1642, 1602, 1499, 1448, 1409, 1374, 1294, 1167, 1110, 1082, 987, 930, 856, 768, 691.

(4-Methylbenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18b)



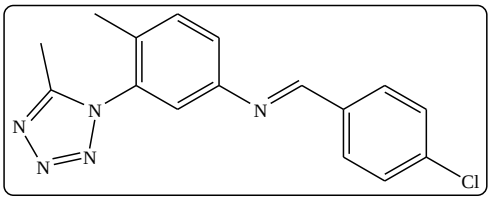
^{1}H-NMR (CDCl$_3$): δ 8.47 (s, 1H), 7.79 (d, 2H), 7.44 (d, 1H), 7.36 (d, 1H), 7.30 (d, 2H), 7.09 (s, 1H), 2.50 (s, 3H), 2.08 (s, 3H), 2.44 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.0, 17.0, 21.0, 119.0, 123.0, 129.0, 129.6, 132.1, 132.3, 133.1, 133.1, 142.2, 151.5, 152.3, 162.4. **IR (KBr, cm^{-1})**: 3057, 2932, 2860, 1634, 1600, 1513, 1456, 1417, 1373, 1282, 1119, 1077, 1019, 981, 799, 762, 720.

(4-Methoxybenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18c)



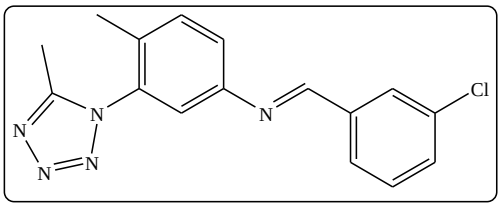
^{1}H-NMR ($CDCl_3$): δ 8.41(s, 1H), 7.85 (d, 2H), 7.43 (d, 1H), 7.35 (d, 1H), 7.07 (s, 1H), 6.99 (d, 2H), 3.90 (s, 3H), 2.50 (s, 3H), 2.07 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.3, 17.6, 55.4, 114.3, 119.1, 123.3, 128.1, 130.9, 131.2, 132.3, 133.2, 151.6, 152.2, 160.1, 162.3. **IR (KBr, cm^{-1})**: 3014, 2953, 1630, 1584, 1491, 1446, 1407, 1381, 1276, 1123, 1079, 1017, 978, 809, 761, 723.

(4-Chlorobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18d)



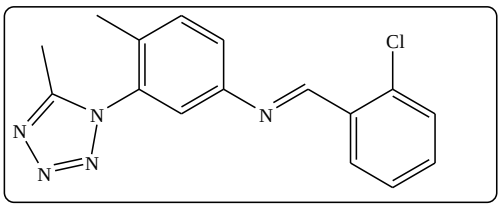
^{1}H-NMR ($CDCl_3$): δ 8.46 (s, 1H), 7.85 (d, 2H), 7.46-7.49 (d, 2H), 7.38 (d, 2H), 7.11 (s, 1H), 2.51 (s, 3H), 2.09 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.1, 16.9, 119.3, 123.4, 129.2, 130.2, 132.4, 132.7, 133.1, 134.1, 138.09, 150.8, 152.5, 160.2. **IR (KBr, cm^{-1})**: 3067, 2961, 1621, 1592, 1498, 1402, 1281, 1121, 1098, 1072, 1003, 846, 762.

(3-Chlorobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18e)



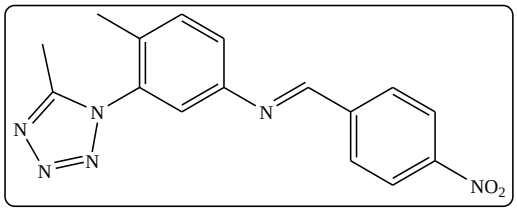
^{1}H-NMR ($CDCl_3$): δ 8.51 (s, 1H), 7.94-7.96 (m, 1H), 7.75 (d, 1H), 7.49-7.53 (m, 3H), 7.37 (d, 1H), 7.11 (s, 1H), 2.52 (s, 3H), 2.11 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.1, 16.9, 119.4, 119.6, 123.4, 123.6, 126.1, 127.4, 128.5, 130.0, 130.2, 131.9, 132.4, 132.6, 132.9, 133.2, 133.3, 133.5, 134.3, 135.2, 137.3, 137.3, 150.0, 150.6, 152.5, 158.6, 160.0. **IR (KBr, cm^{-1})**: 3054, 2948, 1626, 1588, 1521, 1495, 1436, 1409, 1372, 1281, 1126, 1073, 1011, 980, 802, 754, 716.

(2-Chlorobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18f)



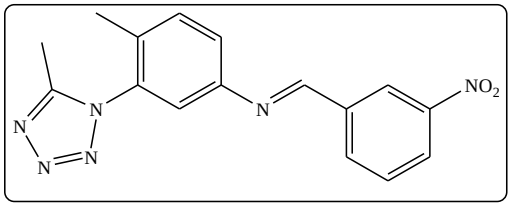
^{1}H-NMR (CDCl$_3$): δ 8.95 (s, 1H), 8.23-8.26 (m, 1H), 7.44-7.47 (m, 3H), 7.39-7.42 (m, 2H), 7.13 (d, 1H), 2.51 (s, 3H), 2.09 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 16.9, 119.7, 123.5, 127.3, 128.6, 130.1, 132.4, 132.6, 132.8, 132.9, 133.2, 136.4, 150.9, 152.5, 158.3. **IR (KBr, cm^{-1})**: 3084, 2937, 1629, 1598, 1509, 1431, 1401, 1370, 1274, 1120, 1059, 1002, 979, 802, 751, 710.

(4-Nitrobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18g)



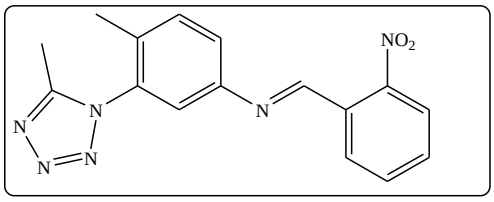
^{1}H-NMR (CDCl$_3$): δ 8.62 (s, 1H), 8.35 (d, 2H), 8.11(d, 2H), 7.52-7.55 (m, 1H), 7.44 (m, 1H), 7.18-7.20 (m, 1H), 2.52 (s, 3H), 2.11 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 17.0, 119.6, 123.5, 124.1, 129.7, 132.6, 140.9, 149.6, 150.0, 152.5, 158.8. **IR (KBr, cm^{-1})**: 3092, 3071, 2939, 2876, 1631, 1587, 1485, 1410, 1355, 1288, 1102, 1051, 985, 853, 813, 746, 710.

(3-Nitrobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18h)



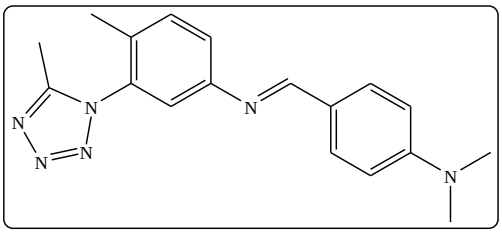
^{1}H-NMR (CDCl$_3$): δ 8.77 (d, 1H), 8.61 (s, 1H), 8.36 (d, 1H); 8.25 (d, 1H), 7.70 (d, 1H), 7.44 (d, 1H), 7.42 (d, 1H), 7.17 (d, 1H), 2.51 (s, 3H), 2.10 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 16.9, 119.6, 123.5, 123.6, 126.1, 130.0, 132.5, 133.3, 133.5, 134.4, 137.3, 148.7, 150.0, 152.5, 158.6. **IR (KBr, cm^{-1})**: 3071, 2957, 1631, 1611, 1529, 1490, 1430, 1352, 1299, 1101, 1078, 1033, 911, 840, 801, 755.

(2-Nitrobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (18i)



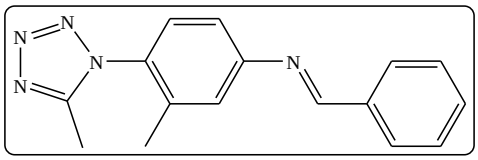
^{1}H-NMR (CDCl$_3$): δ 9.00 (s, 1H), 8.29 (d, 1H), 8.12 (d, 1H), 7.78-7.80 (m, 1H), 7.69-7.72 (m, 1H), 7.50-7.52 (m, 1H), 7.44-7.46 (m, 1H), 7.19 (d, 1H), 2.52 (s, 3H), 2.11 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 17.0, 120.1, 123.3, 124.7, 129.8, 130.5, 131.8, 132.5, 133.2, 133.6, 133.8, 149.3, 150.2, 152.5, 157.4. **IR (KBr, cm^{-1})**: 3093, 2989, 1628, 1581, 1508, 1411, 1355, 1305, 1257, 1102, 1089, 1024, 985, 853, 750, 710.

(4-Dimethylaminobenzylidene)(4-methyl-3-(5-methyl-1H-tetrazol-1-yl)phenyl) amine (18j)



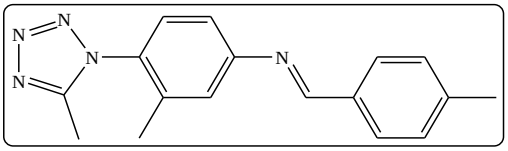
^{1}H-NMR (CDCl$_3$): δ 8.34 (s, 1H), 7.76 (d, 2H), 7.41 (d, 1H), 7.35 (d, 1H), 7.06 (d, 1H), 6.74 (d, 2H), 3.08 (s, 6H); 2.49 (s, 3H), 2.06 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 16.8, 40.1, 111.5, 119.3, 123.6, 123.7, 130.8, 131.1, 132.2, 133.0, 152.2, 152.5, 152.9, 161.3. **IR (KBr, cm^{-1})**: 3063, 2986, 2939, 1625, 1584, 1501, 1441, 1403, 1364, 1299, 1177, 1106, 1080, 985, 931, 855, 767, 690.

(Benzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19a)



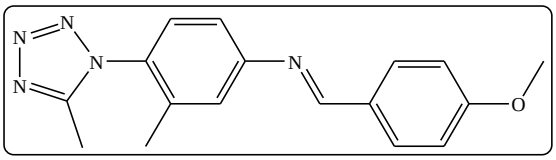
^{1}H-NMR (CDCl$_3$): δ 8.44 (s, 1H), 7.89-7.92 (m, 2H), 7.51-7.54 (m, 4H), 7.46-7.48 (m, 1H); 7.11-7.13 (m, 1H), 2.50 (s, 3H), 2.01 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 17.4, 118.9, 123.2, 127.9, 129.1, 132.0, 132.4, 132.6, 133.5, 135.6, 151.3, 152.5, 161.1. **IR (KBr, cm^{-1})**: 3047, 2955, 1609, 1589, 1504, 1451, 1411, 1366, 1293, 1170, 1111, 1080, 984, 931, 853, 765, 690.

(4-Methylbenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19b)



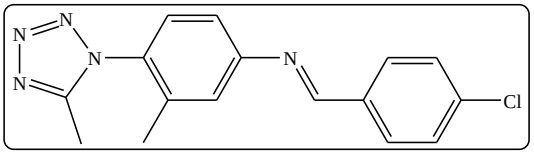
^{1}H-NMR (CDCl$_3$): δ 8.45 (s, 1H), 7.83 (d, 2H), 7.33-7.35 (m, 2H), 7.17-7.19 (m, 3H), 2.49 (s, 3H), 2.46 (s, 3H), 2.10 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.0, 17.1, 21.2, 119.2, 123.0, 129.0, 129.7, 132.1, 132.3, 133.1, 133.1, 142.4, 151.2, 152.7, 162.0. 2.46 (s, 3H), 2.10 (s, 3H). **^{13}C NMR (CDCl$_3$)**: δ 9.0, 17.1, 21.2, 119.2, 123.0, 129.0, 129.7, 132.1, 132.3, 133.1, 133.1, 142.4, 151.2, 152.7, 162.0.

(4-Methoxybenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19c)



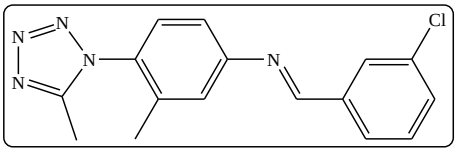
^{1}H-NMR ($CDCl_3$): δ 8.44 (s, 1H), 7.83 (d, 2H), 7.41- 7.44 (m, 1H), 7.33-7.35 (m, 1H), 7.06-7.09 (m, 1H), 6.95-6.97 (m, 2H), 3.96 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.1, 17.2, 55.2, 115.0, 119.0, 123.1, 128.2, 129.3, 130.2, 132.1, 133.0, 151.5, 152.6, 160.2, 161.9. **IR (KBr, cm^{-1})**: 3044, 2937, 1636, 1601, 1591, 1510, 1494, 1451, 1402, 1378, 1281, 1117, 1073, 1021, 974, 806, 757, 721.

(4-Chlorobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19d)



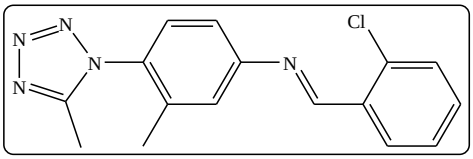
^{1}H-NMR ($CDCl_3$): δ 8.45 (s, 1H), 7.87 (d, 2H), 7.39 (d, 2H), 7.29-7.32 (m, 2H), 7.12 (d, 1H), 2.53 (s, 3H), 2.10 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.1, 17.0, 119.6, 123.8, 129.5, 130.2, 132.4, 132.7, 133.2, 134.2, 138.3, 151.0, 152.7, 160.3. **IR (KBr, cm^{-1})**: 3065, 2964, 1620, 1521, 1496, 1400, 1285, 1126, 1093, 1033, 1000, 842, 825.

(3-Chlorobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19e)



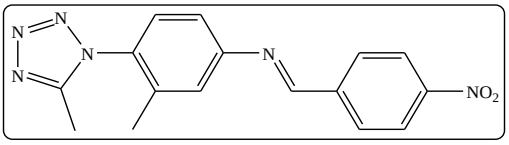
^{1}H-NMR ($CDCl_3$): δ 8.44 (s, 1H), 7.93-7.95 (m, 1H), 7.72-7.74 (m, 1H), 7.47-7.51 (m, 3H), 7.35 (d, 1H), 7.09 (d, 1H), 2.51 (s, 3H), 2.10 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.1, 17.0, 118.8, 119.6, 123.4, 128.7, 130.0, 131.9, 132.4, 133.4, 134.4, 135.2, 137.5, 150.0, 150.6, 160.1. **IR (KBr, cm^{-1})**: 3051, 2942, 1621, 1601, 1583, 1516, 1492, 1456, 1402, 1366, 1276, 1121, 1067, 1013, 977, 801, 751, 719.

(2-Chlorobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19f)



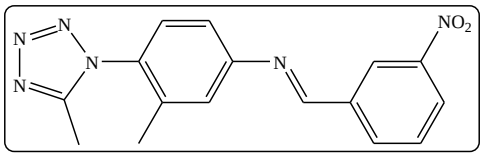
^{1}H-NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.29-8.31 (m, 1H), 7.42-7.46 (m, 3H), 7.37-7.39 (m, 2H), 7.12 (d, 1H), 2.50 (s, 3H), 2.10 (s, 3H). **^{13}C-NMR (CDCl)**: δ 9.1, 17.0, 119.7, 123.5, 127.2, 128.6, 130.1, 132.4, 132.6, 132.7, 132.9, 133.1, 136.3, 151.0, 152.5, 158.3. **IR (KBr, cm^{-1})**: 3080, 2931, 1624, 1592, 1573, 1504, 1501, 1425, 1402, 1375, 1271, 1121, 1062, 1007, 983, 803, 753, 712.

(4-Nitrobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19g)



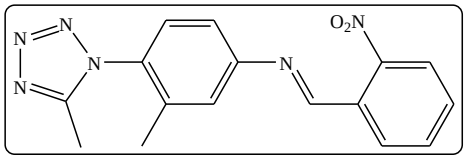
^{1}H-NMR (CDCl$_3$): δ 8.60 (s, 1H), 8.37 (d, 2H), 8.13 (d, 2H), 7.55-7.58 (m, 1H), 7.46-7.48 (m, 1H), 7.19-7.21 (m, 1H), 2.53 (s, 3H), 2.12 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 17.0, 119.6, 123.5, 124.2, 129.5, 132.5, 140.9, 149.7, 150.1, 152.5, 158.8. **IR (KBr, cm^{-1})**: 3086, 3066, 2941, 1637, 1602, 1585, 1503, 1489, 1411, 1350, 1291, 1101, 1050, 986, 855, 810, 749, 711.

(3-Nitrobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19h)



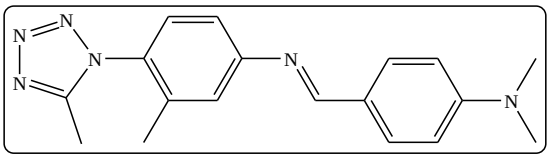
^{1}H-NMR (CDCl$_3$): δ 8.78 (d, 1H), 8.60 (s, 1H), 8.34 (d, 1H), 8.23 (d, 1H), 7.72 (d, 1H), 7.45 (d, 1H), 7.41 (d, 1H), 7.15 (d, 1H), 2.51 (s, 3H), 2.11 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 17.0, 119.6, 123.5, 123.6, 126.1, 130.0, 132.5, 133.2, 133.5, 134.4, 137.3, 148.7, 150.0, 152.5, 158.6. **IR (KBr, cm^{-1})**: 3073, 2961, 1629, 1608, 1589, 1522, 1498, 1431, 1353, 1301, 1103, 1082, 1030, 915, 845, 805, 750 cm^{-1}.

(2-Nitrobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (19i)



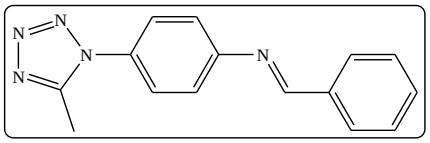
^{1}H-NMR (CDCl$_3$): δ 8.98 (s, 1H), 8.27 (d, 1H), 8.13 (d, 1H), 7.73-7.75 (m, 1H), 7.67-7.70 (m, 1H), 7.52-7.55 (m, 1H), 7.42-7.45 (m, 1H), 7.21 (d, 1H), 2.51 (s, 3H), 2.10 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 16.9, 120.1, 123.3, 124.7, 129.8, 130.6, 130.8, 132.4, 133.3, 133.6, 133.8, 149.3, 150.2, 152.5, 157.5. **IR (KBr, cm^{-1})**: 3088, 2979, 1638, 1601, 1586, 1511, 1499, 1413, 1349, 1307, 1281, 1250, 1100, 1090, 1023, 980, 851, 753, 709.

(4-Dimethylaminobenzylidene)(3-methyl-4-(5-methyl-1H-tetrazol-1-yl) phenyl)amine (19j)



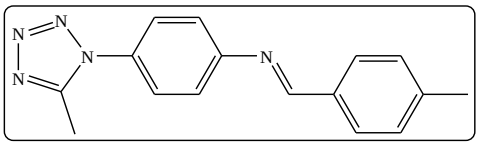
^{1}H-NMR (CDCl$_3$): δ 8.36 (s, 1H), 7.77 (d, 2H), 7.43 (d, 1H), 7.33 (d, 1H), 7.05 (d, 1H), 6.75 (d, 2H), 3.09 (s, 6H), 2.47 (s, 3H), 2.08 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 16.9, 40.1, 111.6, 119.3, 123.6, 123.7, 130.8, 131.0, 132.2, 132.9, 152.2, 152.6, 152.9, 161.7. **IR (KBr, cm^{-1})**: 3066, 2976, 2934, 1623, 1600, 1580, 1505, 1446, 1409, 1361, 1297, 1175, 1102, 1078, 981, 850, 766, 694.

(Benzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20a)



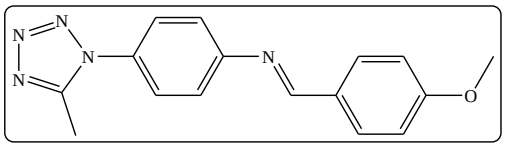
^{1}H-NMR (CDCl$_3$): δ 8.43 (s, 1H), 7.46- 7.52 (m, 5H), 7.31 (d, 2H), 7.19 (d, 2H), 2. 48 (s, 3H), 2.07 (s, 3H). **^{13}C-NMR (CDCl)**: δ 9.1, 114.6, 119.3, 128.6, 129.2, 132.2, 132.4, 133.0, 135.1, 152.0, 161.2. **IR (KBr, cm^{-1})**: 1627, 1581, 1499, 1453, 1410, 1271, 1092, 1000, 841, 695.

(4-Methylbenzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20b)



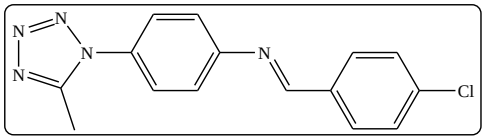
^{1}H-NMR (CDCl$_3$): δ 8.39 (s, 1 H), 7.76 (d, 2 H), 7.43 (d, 2H), 7.33 (d, 2H), 7.18 (d, 2H); 2.49 (s, 3H), 2.39 (s, 3 H), 2.10 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.0, 21.6, 119.9, 125.7, 128.9, 129.2, 131.8, 133.7, 141.8, 152.2, 152.8, 160.3. **IR (KBr, cm^{-1})**: 1597, 1487, 1397, 1269, 1096, 1002, 837, 690.

(4-Methoxybenzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20c)



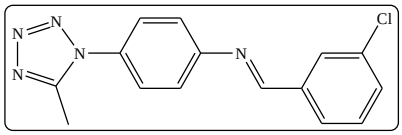
^{1}H-NMR (CDCl$_3$): δ 8.40 (s, 1H), 7.83 (d, 2H), 7.36 (d, 1H), 7.21 (d, 2H), 6.98 (d, 2H), 3.92 (s, 3H), 2.08 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.0, 55.4, 119.4, 123.7, 130.2, 131.1, 132.9, 133.8, 151.1, 152.4, 162.2. **IR (KBr, cm^{-1})**: 3069, 1587, 1490, 1403, 1252, 1096, 1005, 836, 683.

(4-Chlorobenzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20d)



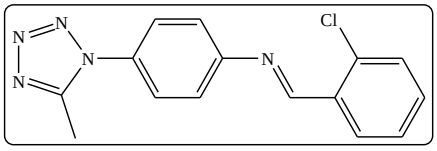
^{1}H-NMR (CDCl$_3$): δ 7.82 (d, 2H), 7.48 (d, 2H), 7.28 (d, 2H), 7.13 (d, 2H), 2.1 (s, 1H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 119.5, 123.3, 129.3, 130.1, 132.4, 138.2, 150.8, 152.5, 160.2. **IR (KBr, cm^{-1})**: 1629, 1524, 1500, 1407, 1279, 1123, 1099, 1063, 1030, 999, 847, 822.

(3-Chlorobenzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20e)



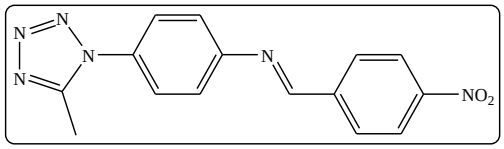
^{1}H-NMR (CDCl$_3$): δ 8.51 (s, 1H), 7.82-7.85 (m, 1H), 7.53-7.55 (m, 3H), 7.46 (d, 2H), 7.11 (d, 2H), 2.11 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 119.4, 119.7, 123.4, 128.5, 130.0, 132.9, 133.4, 133.9, 137.4, 150.1, 151.9, 160.8. **IR (KBr, cm^{-1})**: 1633, 1527, 1503, 1405, 1273, 1128, 1097, 1068, 1027, 995, 854, 820, 717.

(2-Chlorobenzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20f)



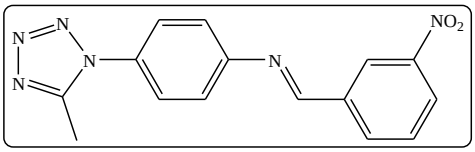
^{1}H-NMR (CDCl$_3$): δ 8.95 (s, 1H), 7.73-7.75 (m, 1H); 7.55 (d, 2H), 7.46-7.49 (m, 2H), 7.39-7.41 (m, 1H); 7.13 (d, 2H), 2.12 (s, 3H) **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 120.1, 121.1, 123.3, 129.4, 130.0, 132.6, 133.3, 133.9, 137.3, 150.0, 152.0, 160.9. **IR (KBr, cm^{-1})**: 1604, 1492, 1406, 1277, 1090, 847, 758, 702.

(4-(5-Methyl-1H-tetrazol-1-yl)phenyl)(4-nitrobenzylidene)amine (20g)



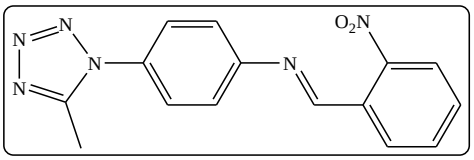
^{1}H-NMR (CDCl$_3$): δ 8.63 (s, 1H), 8.32 (d, 2H), 8.11 (d, 2H), 7.52 (dd, 2H), 7.40 (d, 2H), 2.11 (s, 3H). **C-NMR (CDCl$_3$)**: δ 9.1, 119.7, 123.1, 129.2, 131.4, 132.4, 133.5, 140.9, 150.1, 152.2, 160.1. **IR (KBr, cm^{-1})**: 3100, 1596, 1506, 1409, 1337, 1162, 1096, 841, 693.

(4-(5-Methyl-1H-tetrazol-1-yl)phenyl)(3-nitrobenzylidene)amine (20h)



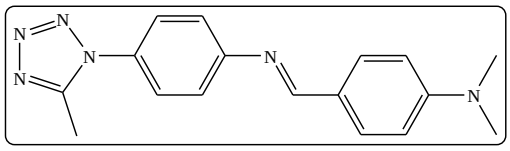
^{1}H-NMR (CDCl$_3$): δ 8.79-8.82 (m, 1H), 8.61 (s, 1H), 7.48-7.52 (m, 3H), 7.38 (d, 2H), 7.28 (d, 2H), 2.10 (s, 3H). **^{13}C-NMR (CDCl$_3$)**: δ 9.1, 119.5, 123.5, 124.2, 128.0, 130.0, 131.6, 133.3, 133.9, 136.0, 148.7, 152.5, 158.6. **IR (KBr, cm^{-1})**: 3106, 2324, 1597, 1485, 1400, 1293, 1097, 1003, 845, 692.

(4-(5-Methyl-1H-tetrazol-1-yl)phenyl)(2-nitrobenzylidene)amine (20i)



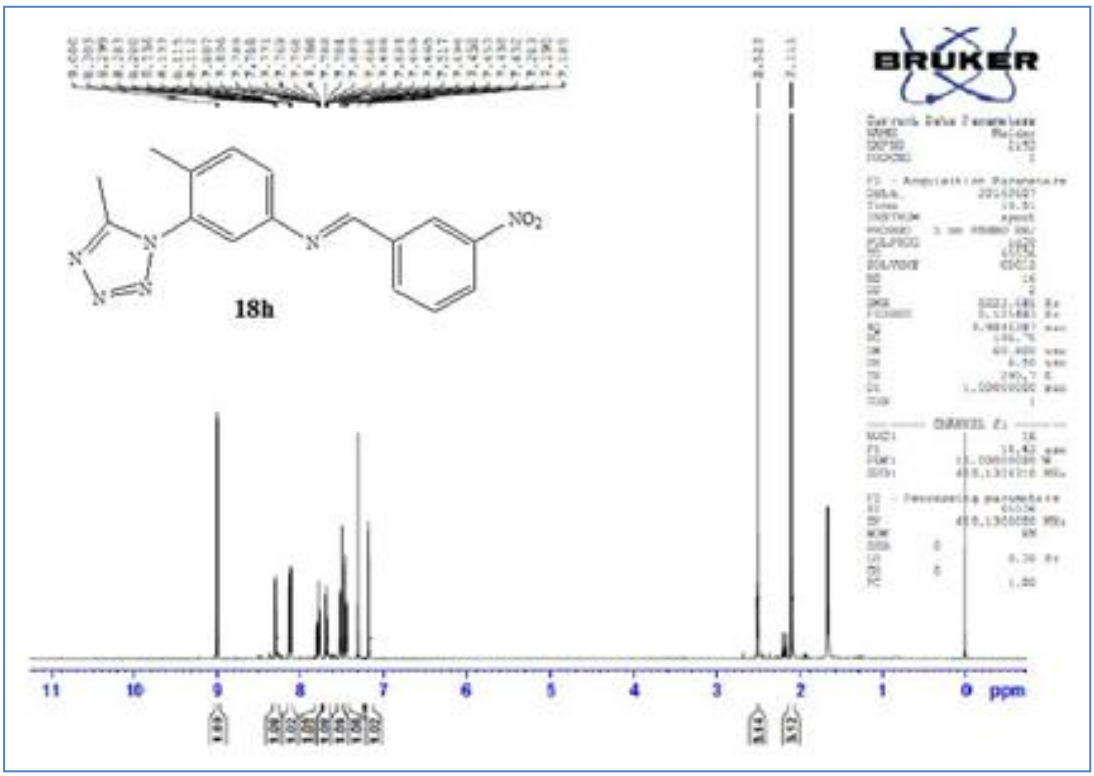
^{1}H-NMR (CDCl$_3$): δ 8.94 (s, 1H), 8.26-8.28 (m, 1H), 7.63-7.68 (m, 2H), 7.51-7.53 (m, 1H), 7.44 (d, 2H), 7.24 (d, 2H), 2.10 (s, 3H). **^{13}C-NMR (CDCl)**: δ 9.1, 119.4, 123.3, 125.1, 129.0, 130.7, 131.1, 133.6, 133.2, 137.4, 149.3, 151.6, 159.7. **IR (KBr, cm^{-1})**: 3076, 1629, 1607, 1494, 1403, 1299, 1105, 1009, 855, 754, 698.

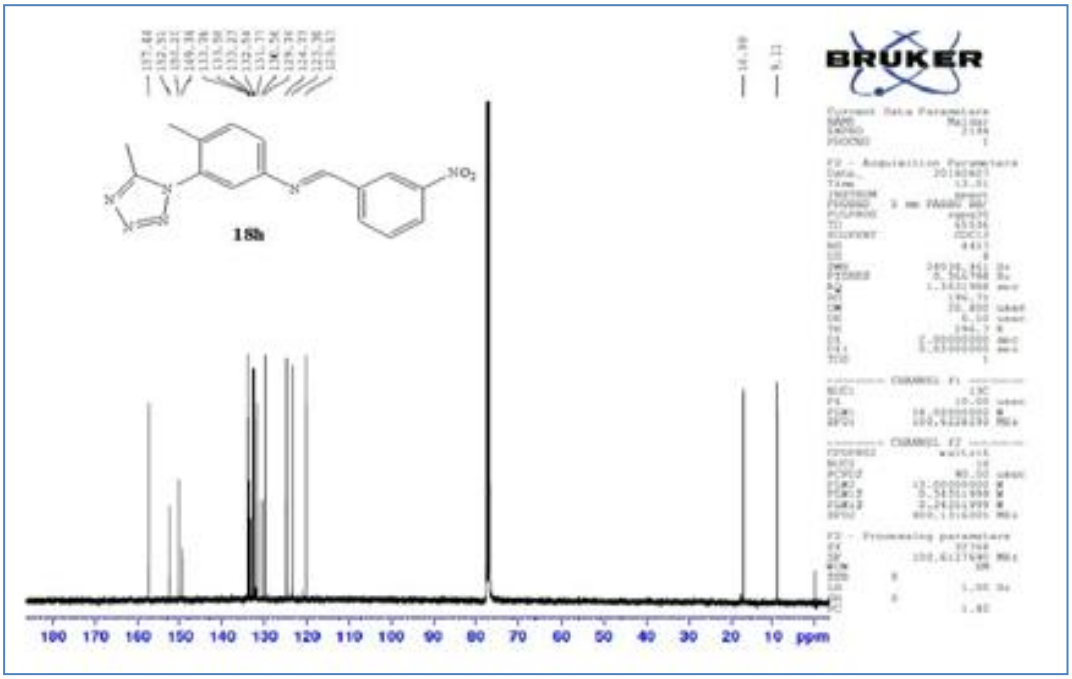
(4-Dimethylaminobenzylidene)(4-(5-methyl-1H-tetrazol-1-yl)phenyl)amine (20j)

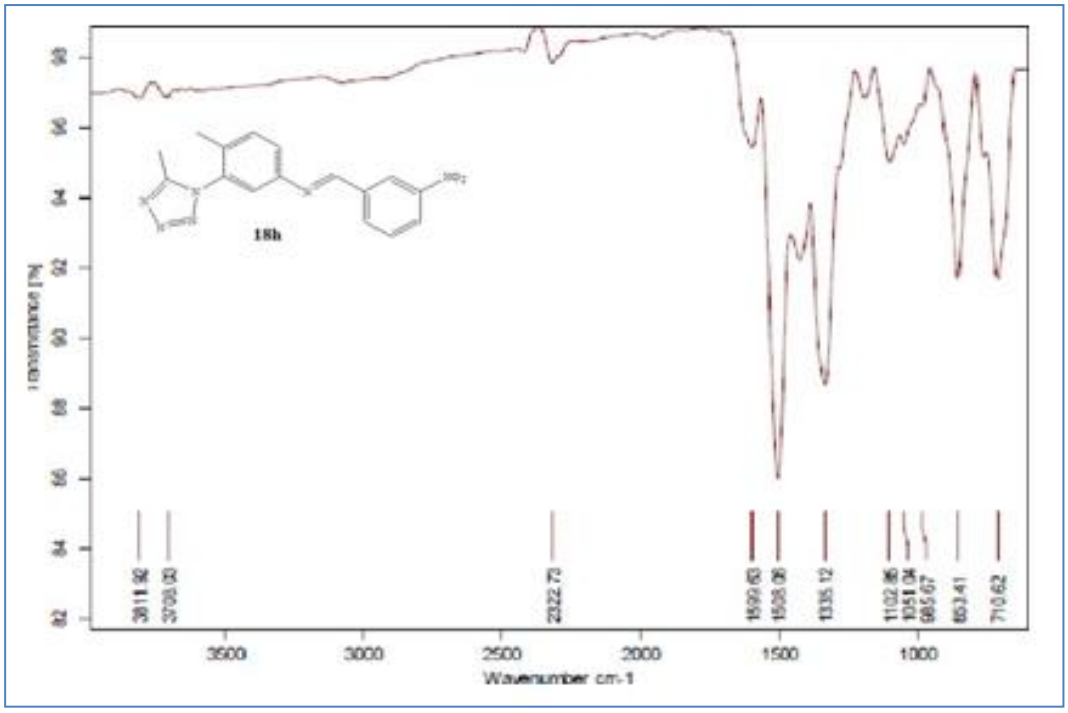


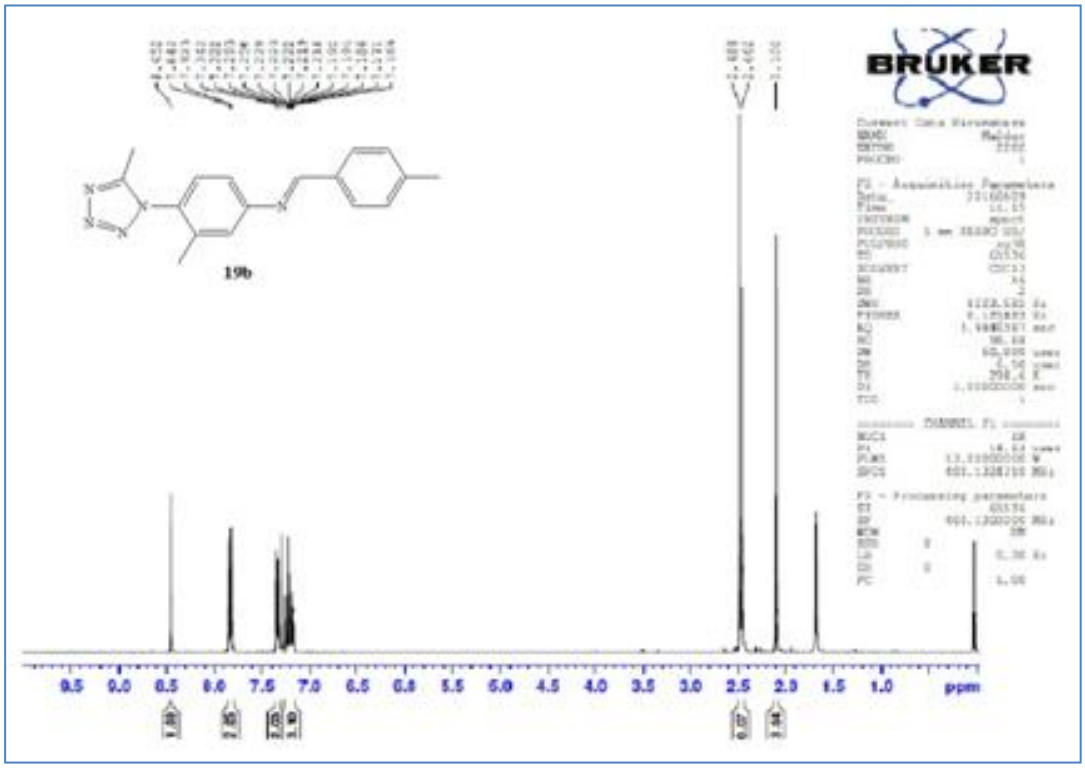
^{1}H-NMR ($CDCl_3$): δ 8.38 (s, 1H), 7.72 (d, 2H), 7.41 (d, 1H), 7.39 (d, 1H), 7.10 (d, 2H), 6.77 (d, 2H), 3.09 (s, 6H), 2.07 (s, 3H). **^{13}C-NMR ($CDCl_3$)**: δ 9.1, 41.1, 111.5, 119.7, 123.1, 130.5, 131.3, 132.1, 132.7, 151.1, 152.4, 161.5. **IR (KBr, cm^{-1})**: 1627, 1629, 1601, 1581, 1502, 1442, 1405, 1359, 1299, 1176, 1108, 1073, 980, 851, 760.

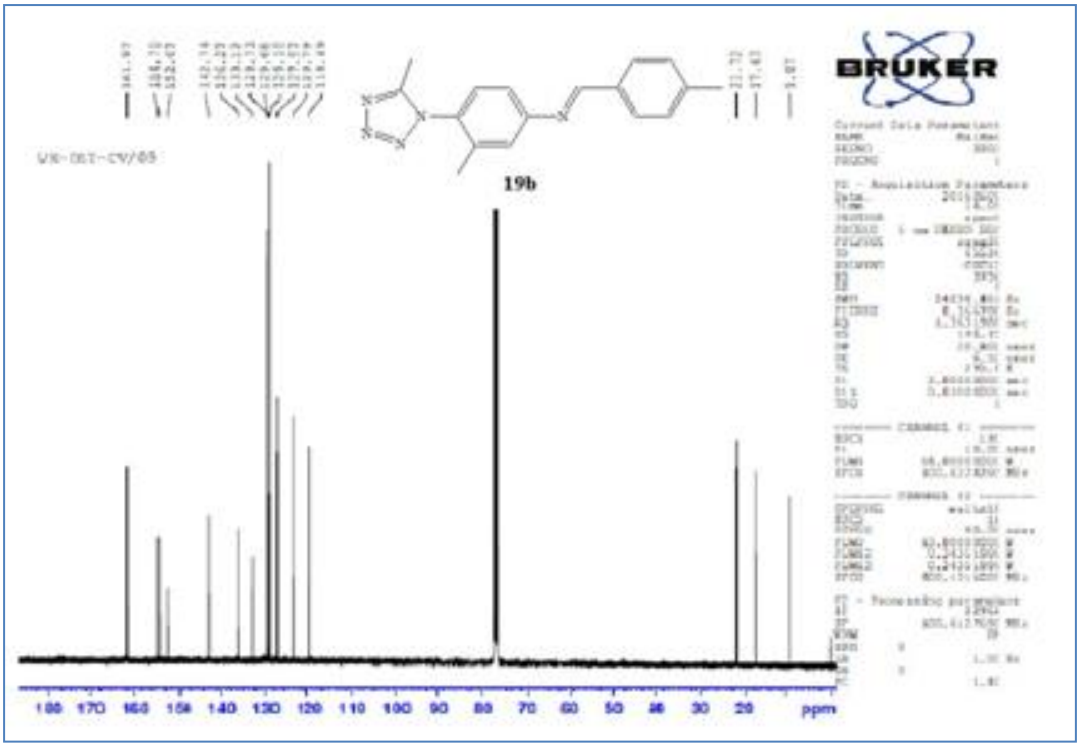
Selected Spectra

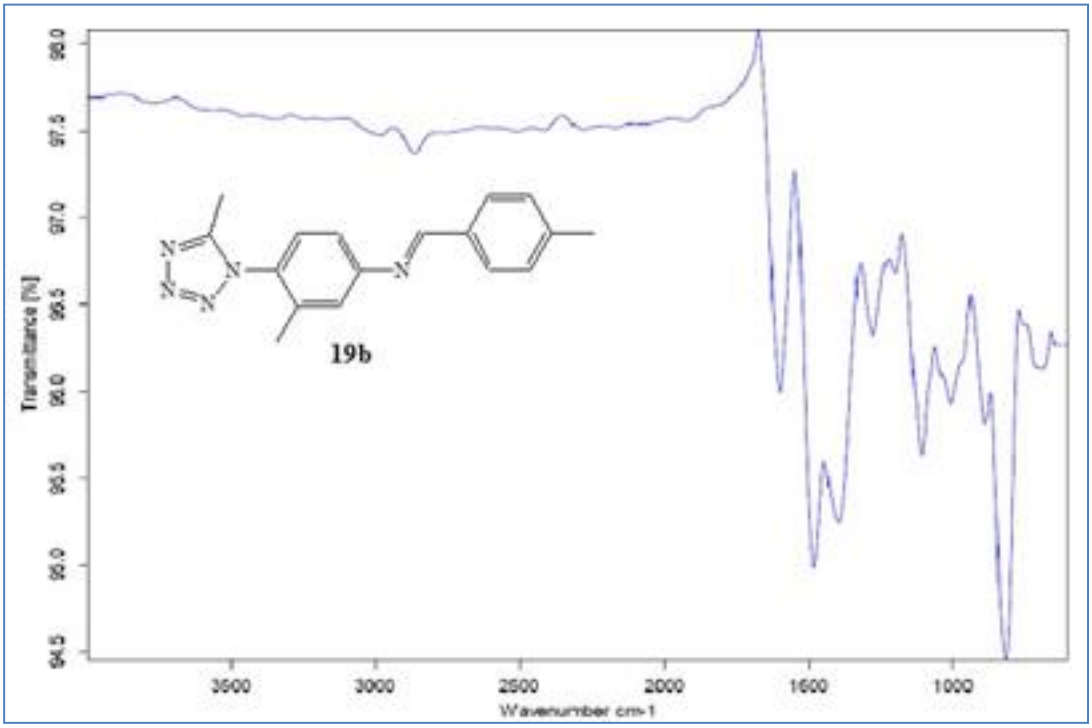





18h
Transmittance [%]
3811.92
3709.30
2322.75
1599.63
1508.08
1335.12
1102.85
1051.04
985.67
853.41
710.62
3500
3000
2500
2000
1500
1000
Wavenumber cm-1


19b
BRUKER
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm





5.5 Conclusion

As the tetrazole scaffolds and Schiff bases are found to show variety of biological activities. The interest has been made towards the synthesis of novel 1, 5-disubstituted tetrazole containing Schiff bases. Herein, we have designed and synthesized for the first time three different series of 1, 5-disubstituted tetrazole containing Schiff bases. In the present work, we have synthesized the novel Schiff bases by reacting 1, 5- disubstituted tetrazole containing

anilines with commercially available substituted aldehydes in ethanol at room temperature. In this synthesis, condensation of 1, 5-disubstituted tetrazole containing aromatic amine with aldehyde was carried without any catalyst. The reaction requires less time when compared with reaction with other heterocyclic amines. The synthesized compounds were characterized by using IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques.

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1,5-Disubstituted Tetrazoles: Synthesis and Characterization

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About Author

Dr. Suresh G. Vedpathak
M.Sc. Ph.D.
Head & Professor
Department of Chemistry,
S.M. Dnyandeo Mohekar Mahavidyalaya, Kalamb,
Dist. Dharashiv 413507 (MS) India.

Dr. Suresh G. Vedpathak is a highly accomplished academician and researcher, currently serving as the Head and Associate Professor in the Department of Chemistry at S.M. Dnyandeo Mohekar Mahavidyalaya, Kalamb. With over 20 years of teaching experience and nine years dedicated to research, he has significantly contributed to the field of heterocyclic chemistry. Dr. Vedpathak has an impressive research portfolio, with more than 20 research papers published in reputed national and international journals. His work focuses on exploring and synthesizing heterocyclic compounds, which hold immense potential in pharmaceuticals and materials science. His commitment to academic excellence is evident through his role as a research guide, currently supervising two Ph.D. scholars in their advanced studies. Beyond teaching and research, Dr. Vedpathak plays a crucial role in mentoring students, guiding them in their academic and professional pursuits. Under his leadership, the Department of Chemistry continues to thrive, fostering an environment that encourages innovation and scientific inquiry. His dedication to the field of chemistry has made a lasting impact on both students and fellow researchers. With a strong focus on research, publication, and student mentorship, Dr. Vedpathak remains an influential figure in the academic community. Through his contributions, he continues to inspire the next generation of chemists while advancing knowledge in heterocyclic chemistry.

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